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HEMOLYTIC STREPTOCOCCIC AND NONSTREPTOCOCCIC DISEASES OF THE RESPIRATORY TRACT

A Comparative Clinical Study

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GREAT interest has been aroused in hemolytic streptococcic infection of the respiratory tract during recent years. This has been the result of the demonstration that such infection frequently initiates a complex nonsuppurative process, of which rheumatic fever is the most important and dramatic manifestation. A recent critical study [1] showed that this disease was invariably preceded by a hemolytic streptococcic infection. In spite of this fact, definitive clinical studies of the nature of streptococcic infection of the respiratory tract are almost nonexistent. The Dicks [2] and Dochez [3] established the fact that scarlet fever is caused by hemolytic streptococci and showed that experimental infection in human beings was not always associated with rash formation. An immunologic explanation of this phenomenon

The laboratories of the Department of Medicine, Stanford University School of Medicine, San Francisco, were made available to the Commission for certain purposes.

Col. T. E. Harwood Jr., Major James Blanton and Capt. Howard Coggeshall assisted in the preparation of this paper. Elizabeth Randall, Viola Ferris, Loraine Kerr and Helen Rantz were responsible for the technical and secretarial work.

This investigation was carried out during a field study by the Commission on Hemolytic Streptococcal Infections, Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army, Preventive Medicine Service, Office of the Surgeon General, United States Army.

1. Rantz, L. A.; Spink, W. W., and Boisvert, P. J.: The Etiology and Pathogenesis of Rheumatic Fever, Arch. Int. Med. **76**:131 (Sept.) 1945.

2. Dick, G. F., and Dick, G. H.: Experimental Scarlet Fever, J. A. M. A. **81**:1166 (Oct. 6) 1923.

3. Dochez, A. R., and Sherman, L.: Significance of Streptococcus Hemolyticus in Scarlet Fever: Preparation of a Specific Anti-Scarlatinal Serum by Immunization of Horse to Streptococcus Hemolyticus-Scarlatinae, J. A. M. A. **82**:542 (Feb. 16) 1924.

was offered. Adequate monographs describing the natural history of scarlet fever are available but deal largely with the disease as observed in children.[4]

The splendid work of Lancefield [5] has demonstrated that nearly all hemolytic streptococcic infections of the respiratory tract in human beings are caused by a single serologic group of the hemolytic streptococci, designated by the letter "A," and that this group may be subdivided into types. Application of these technics has yielded much new information. It has been shown clearly that certain types of hemolytic streptococci of group A, now causing much disease in military personnel, are incapable of inducing rash formation in persons with positive Dick reactions, who presumably are susceptible.[6] Strains of these types have been responsible for 90 per cent of all streptococcic infections in certain areas. Furthermore, infection by definitely scarlatinogenic strains has been associated with rash formation in only about 25 per cent of young adults in the armed forces. A similar situation almost certainly exists in the civilian population.

The problem of streptococcic infection of the respiratory tract is therefore that of a disease not associated with a scarlatiniform rash. Insufficient recognition has been afforded this fact, and comprehensive descriptions of the disease are virtually nonexistent, except for those of Bloomfield and his associates,[7] who have described all the salient features of streptococcic infection, have pointed out that the disease process ordinarily assumes the form of an exudative tonsillitis and have claimed that tonsillectomy confers a high degree of immunity against such infection. It is difficult to add other than further documentation to these excellent descriptions of tonsillitis. The authors did not, however, have the opportunity to study systematically a large number of persons suffering from infection of the respiratory tract in an area in which streptococcic infection was exceedingly common. They were unable, therefore, to determine the frequency of streptococcic

4. Escherich, T., and Schick, B.: Scharlach, Vienna, A. Hölder, 1912. Trask, J.: Scarlet Fever, in Christian, H. A., and MacKenzie, J.: Oxford Medicine, New York, Oxford University Press, 1940, vol. 5, chap. 21, p. 519.

5. Lancefield, R. C.: Specific Relationship of Cell Composition to Biological Activity of Hemolytic Streptococci, in Harvey Lectures, 1940-1941, Baltimore, Williams & Wilkins Company, 1941, vol. 36, p. 251.

6. Hamburger, M., Jr.; Hilles, C. H.; Hamburger, V. G.; Johnson, M. A., and Wallin, J. G.: Ability of Different Types of Hemolytic Streptococci to Produce Scarlet Fever, J. A. M. A. **124**:564 (Feb. 26) 1944.

7. (*a*) Felty, A. R., and Hodges, A. B.: A Clinical Study of Acute Streptococcus Infection of the Pharyngeal Lymphoid Tissue (Acute Follicular Tonsillitis), Bull. Johns Hopkins Hosp. **34**:330, 1923. (*b*) Bloomfield, A. L.: Streptococcal Infections, in Blumer, G.: Practitioners Library of Medicine and Surgery, New York, D. Appleton-Century Company, Inc., 1933, chap. 15, sect. 2, p. 235. (*c*) Bloomfield, A. L.: Differentiation of the Common Varieties of Sore Throat, Stanford M. Bull. **1**:199, 1943.

infection in persons who had undergone tonsillectomies or the importance of exudate as a diagnostic sign in these circumstances.

One critical study of the nature of streptococcic and nonstreptococcic disease has been published.[8] The authors characterized diseases of the respiratory tract in part and emphasized the fact that exudative tonsillitis may occur in the absence of streptococcic infection. They were greatly handicapped by the fact that the number of patients with streptococcic disease in their group was extremely small. An unfortunate confusion has resulted from their report since the impression was given that the clinical diagnosis of streptococcic infection, even though aided by bacteriologic study of the nasopharyngeal flora, is virtually impossible.

It is the purpose of this paper to present and analyze the clinical and laboratory data obtained during the study of a large number of infections of the respiratory tract occurring in military personnel. The infections will be discussed in groups as they were classified immediately after the completion of the initial clinical and laboratory study, and it will be demonstrated that the accuracy of diagnosis was great. The incidence and the value of the various signs and symptoms of diagnostic importance will be described statistically and a composite picture of each disorder presented. A complete description of the natural history of hemolytic streptococcus infection will be presented elsewhere.

Atypical and confusing examples of both streptococcic and nonstreptococcic disease were frequently discovered, and the general conclusions in the previously mentioned work[8] were confirmed. These assume a different and clinically more encouraging perspective when considered in relationship to the data obtained in this study of a large number of infections of the respiratory tract, which occurred in an area in which streptococcic disease was common. This probably resembles situations often encountered in the northern United States. In this regard it is important to know that, in spite of the fact that a large number of streptococcic infections occurred during the study period, no true epidemic was established, since fourteen serologic types of streptococci caused infection in more than 5 patients each and a total of twenty-six different types were isolated. Furthermore, the population involved was composed largely of well seasoned troops rather than the new recruits who have been shown repeatedly to be highly susceptible to

8. Commission on Acute Respiratory Diseases: Endemic Exudative Pharyngitis and Tonsillitis, J. A. M. A. **125**:1163 (Aug. 26) 1944. Another similar study has been recently described (Keith, J. D., and Carpenter, J.: The Diagnosis of Haemolytic Streptococcal Infection in Acute Nasopharyngitis, Canad. Pub. Health J. **37**:127, 1946).

all types of infection of the respiratory tract.[9] It is believed that the report of our experience more nearly simulates what may be expected in a civilian population than do other descriptions of the disease among military personnel.

METHODS

Plan of Study.—All patients with acute disease of the respiratory tract of any type admitted to a large station hospital were studied. Dispensary physicians ordinarily requested hospitalization for all men with symptoms of disease of the respiratory tract whose temperatures were discovered to be elevated to 100 F. or more. Each patient was seen during the first hospital day by one of us, and the clinical and laboratory studies described in the following paragraphs were instituted.

Clinical Observations.—A history was obtained when each patient was first seen, which was adequate to evaluate the illness. Specific questions were asked in regard to the presence and severity of the following features of the disease, in addition to others:

1. Sore throat, which was rated as 1 plus (slightly sore) to 3 plus (swallowing painful and difficult).
2. Cough.
3. Headache.
4. Chills.
5. Generalized aching.
6. Hoarseness.
7. Coryza.

A physical examination was performed at the same time, special attention being given to the presence of the following signs:

1. Tonsils.
2. Exudate. This sign was graded from 1 plus (small flecks of white material on the tonsils, tonsillar tags or posterior pharyngeal walls) to 3 plus (large confluent areas of white material, often covering the whole tonsil and spreading onto the pharyngeal wall).
3. Abnormal redness of the tonsils and tissues of the anterior and posterior pharynx. This sign was graded from 1 plus (slightly red with engorgement of the blood vessels of the mucosa) to 3 plus (fiery red).
4. Edema of the tonsils and pharyngeal tissues. This sign was graded from 1 plus (slight edema) to 3 plus (massive edema).
5. Tender anterior cervical glands. This sign was graded from 1 plus (definite tenderness of the glands without great enlargement) to 3 plus (the glands greatly enlarged and extremely tender).
6. Scarlatiniform rash.

Cultures of Material from the Throat and the Nose.—The nose and the throat of each patient were swabbed at the time of the initial examination, and cultures were prepared suitable for the isolation of hemolytic streptococci. The methods used will be described elsewhere. Additional swabbings were carried out at

9. Wheeler, S. M., and Jones, T. D.: Factors in the Control of the Spread of Acute Respiratory Infections with Reference to Streptococcal Illness and Acute Rheumatic Fever, Am. J. M. Sc. **209**:58, 1945.

frequent intervals if hemolytic streptococci were present initially or if the diagnosis remained doubtful. All the isolated hemolytic streptococci were classified serologically into groups and types by means of the precipitin technics of Lancefield.[10]

Cultures were recorded as:

1. Negative—No group A hemolytic streptococci recovered.
2. 1 plus—A few group A hemolytic streptococci were isolated.
3. 2 plus—Moderate numbers of hemolytic streptococci were isolated. The predominant flora was composed of other organisms.
4. 3 plus—Many hemolytic streptococci were present and were the predominant organisms, but other organisms were also recovered in considerable numbers.
5. 4 plus—Group A hemolytic streptococci were isolated in very large numbers and were the predominant organisms in the nasopharyngeal flora. Frequently they appeared to be present in pure culture.

All group A hemolytic streptococcus infections will be considered together, regardless of the serologic type of the infectious agent. Full details of the relationship of the type to various clinical and immunologic phenomena will be presented elsewhere.

Leukocyte Counts and Erythrocyte Sedimentation Rates.—The total leukocyte count and the erythrocyte sedimentation (Westergren) rate were determined on the second hospital day for all patients believed to have hemolytic streptococcus infections, for many patients for whom the diagnosis remained doubtful and for a small group of persons in whom definite nonstreptococcic infection had occurred.

Immunologic Study.—The antistreptolysin and the antifibrinolysin of the serum and the plasma of many patients were measured on approximately the second, ninth and twenty-first days of illness by methods described elsewhere.[11] Full details of these immunologic observations will be presented in another report. For this report it is necessary only to define the increase of the antibody which has been regarded as significant for the establishment of the etiologic relationship between an infectious disease and the hemolytic streptococci. It is believed that a 50 per cent increment in the antistreptolysin titer or an eight hour prolongation of the time for lysis in the determination of antifibrinolysin is to be regarded as adequate for this purpose.

No details will be given in the body of the paper as to the nature and the degree of the antibody response which, if stated to be present, may be assumed to have involved an increase as great as or greater than that previously described in the amount of the circulating antistreptolysin, the antifibrinolysin or both.

Selection of Cases.—Each hospitalized patient suffering from a disease of the respiratory tract during the study period was examined initially by the technic described earlier. For the purpose of clarity in this presentation, all examples of the common communicable diseases, ulcerative tonsillitis (Vincent's disease) and bacterial or diagnosed primary atypical pneumonia, have been excluded from consideration. Many men in whom the latter disease occurred in a mild and unrecognized form have, without doubt, been included in the group of patients with nonstreptococcic infections.

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10. Lancefield.[5] Most of the typing serums were made available through the generosity of Dr. Rebecca Lancefield.

11. Rantz, L. A., and Randall, E.: A Modification of the Technic for Determination of the Antistreptolysin Titer, Proc. Soc. Exper. Biol. & Med. **59**:22, 1945. Boisvert, P. J.: The Streptococcal Antifibrinolysin Test in Clinical Use, J. Clin. Investigation **19**:65, 1940.

TABLE 1.—*Symptoms and Physical Signs in Patients with Hemolytic Streptococcic and Nonstreptococcic Diseases of the Respiratory Tract*

	Nonstreptococcic Disease		Group A Carriers		Hemolytic Streptococcic Disease with Antibody Response		Hemolytic Streptococcic Disease Without Antibody Response		Scarlet Fever		Hemolytic Streptococcic Disease, Tonsils Intact		Hemolytic Streptococcic Disease, Tonsils Removed	
	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
Total patients	871	100.0	93	100.0	300	100.0	42	100.0	27	100.0	201	100.0	99	100.0
Symptoms														
Sore throat														
Absent	416	47.7	47	50.5	24	8.0	2	4.7	1	3.7	12	5.9	12	12.1
1 plus	162	18.6	21	22.6	40	13.3	6	14.3	3	11.1	24	10.9	16	16.2
2 plus	149	17.1	18	19.4	88	29.4	16	38.1	6	22.6	61	30.3	27	27.2
3 plus	144	16.6	7	7.5	148	49.4	18	43.0	17	63.0	104	51.7	44	44.5
Cough														
Present	726	83.3	29	31.2	127	42.3	17	40.4	12	45.0	84	41.8	41	41.4
Severe	210	24.1	24	25.8	7	2.3	2	4.7	0	0.0	5	2.5	2	2.0
Headache														
Present	537	62.3	55	59.1	233	77.8	28	66.6	12	45.0	177	78.1	76	76.6
Severe	53	6.8	7	7.5	36	12.0	3	7.1	0	0.0	22	10.9	14	14.1
Generalized aching	322	37.0	34	36.8	178	59.4	22	52.4	14	51.9	110	54.6	68	68.7
Coryza	316	36.2	34	36.5	65	21.6	9	21.4	8	29.6	47	23.4	18	18.2
Chills	241	27.6	26	28.0	189	63.0	19	45.3	18	66.6	121	60.3	68	68.7
Hoarseness	115	13.2	10	10.8	3	1.0	0	0.0	0	0.0	1	0.5	2	2.0
Physical signs														
Exudate														
Absent	827	95.0	88	94.6	113	37.7	13	30.9	13	48.2	53	26.4	60	60.6
1 plus	29	3.3	5	5.4	55	18.3	5	11.9	3	11.1	35	17.4	20	20.2
2 plus	12	1.4	0	0.0	73	24.3	8	19.1	6	22.2	58	28.8	15	15.1
3 plus	3	0.3	0	0.0	59	19.7	16	38.1	5	18.5	55	27.4	4	4.0
Edema														
Absent	562	64.5	56	60.2	43	14.3	5	11.9	5	18.5	22	10.9	21	21.2
1 plus	214	24.6	29	31.2	82	27.3	7	16.7	5	18.5	47	23.4	35	35.4
2 plus	85	9.7	8	8.6	113	37.7	15	35.7	12	44.5	79	39.3	34	34.3
3 plus	10	1.2	0	0.0	62	20.7	15	35.7	5	18.5	53	26.4	9	9.1
Redness														
Absent	366	42.0	37	39.9	10	3.3	1	2.4	0	0.0	6	2.9	4	4.0
1 plus	298	34.2	32	34.4	39	13.0	3	7.1	4	14.8	22	10.9	17	17.2
2 plus	144	16.5	18	19.3	95	31.6	17	40.5	9	33.3	56	27.8	39	39.4
3 plus	63	7.3	6	6.4	156	52.0	21	50.0	14	51.9	117	58.3	39	39.4
Adenitis														
Present	116	13.6	12	12.9	243	80.9	37	88.1	23	85.2	170	84.6	73	73.8
Severe	15	1.7	0	0.0	131	43.6	17	40.5	10	37.0	102	50.8	29	29.3
Height of fever														
Afebrile	273	31.4	27	29.1	7	2.3	0	0.0	0	0.0	5	2.5	2	2.0
99 to 99.9 F	186	21.4	30	32.1	13	4.3	3	7.1	0	0.0	9	4.5	4	4.0
100 to 100.9 F	149	17.1	11	11.8	31	10.3	7	16.7	3	11.1	20	9.9	11	11.0
101 to 101.9 F	111	12.7	10	10.8	59	19.6	9	21.4	4	14.8	39	19.4	20	20.2
102 to 102.9 F	94	10.8	10	10.8	70	23.3	10	23.8	6	22.2	48	23.8	22	22.2
103 F. and up	58	6.5	5	5.4	120	40.0	13	30.9	14	51.9	80	39.9	40	40.5

Eighty-one additional patients, from whose throats hemolytic streptococci of groups other than A were isolated, have not been considered. In certain patients the streptococci were etiologically responsible for the disease process, and in others in whom a "virus type" of disease had occurred they were present fortuitously in the nasopharynx. The presence of such streptococci in the throat constitutes a problem in the study of disease of the respiratory tract and will be discussed elsewhere because of the difficulties of intepretation and for the sake of simplicity.

The remaining patients have been divided into groups exactly as they were classified after the completion of the initial clinical and bacteriologic study. Sixty-eight patients, believed on clinical and bacteriologic grounds to have had hemolytic streptococcus infections, have been omitted because serial antibody determinations were not obtained.

HEMOLYTIC STREPTOCOCCIC INFECTION

Hemolytic streptococci of group A were isolated from the throats or the nasopharynges of 342 men whose disease of the respiratory tract was believed, on clinical grounds, to be the result of infection by these organisms. An antibody response was demonstrated in 300, or 87.7 per cent, of the patients, indicating that the diagnosis was usually accurate. Those in whom an increase in antibody failed to develop cannot be proved to have streptococcic disease, but it is known [12] that in from 10 to 20 per cent of all instances of scarlet fever the patients fail to exhibit an antistreptolysin or antifibrinolysin response. Infection by streptococci cannot be excluded on the basis of the study of these antibodies. The critical clinical study is based on the 300 patients in whom the disease was proved to be streptococcic, but the data obtained for the additional 42 are included for inspection by interested persons. There is a striking parallelism between the manifestations of the infectious process in the two groups.

The significant data obtained during this study of group A hemolytic streptococcus infection are presented under various categories in the last five columns of tables 1 and 2. This information will now be described and discussed.

Symptoms.—Sore throat was the most characteristic symptom of hemolytic streptococcus disease of the respiratory tract. It was severe or extremely severe in 78.8 per cent of all patients. Swallowing was unusually difficult for these men, and even fluids were frequently refused. The frequency of occurrence of this symptom is indicated by the fact that it was absent in only 8 per cent of all patients.

12. Mote, R. J., and Jones, T. D.: Studies of Hemolytic Streptococcal Antibodies in Control Groups, Rheumatic Fever and Rheumatoid Arthritis: II. The Frequency of Antistreptolysin "O," Antifibrinolysin and Precipitating-Antibody Responses in Scarlet Fever, Hemolytic Streptococcal Infections and Rheumatic Fever, J. Immunol. **41**:35, 1941.

TABLE 2.—*Laboratory Data for Patients with Hemolytic Streptococcic and Nonstreptococcic Diseases of the Respiratory Tract*

	Nonstreptococcic Disease		Group A Carriers		Hemolytic Streptococcic Disease with Antibody Response		Hemolytic Streptococcic Disease Without Antibody Response		Scarlet Fever		Hemolytic Streptococcic Disease, Tonsils Intact		Hemolytic Streptococcic Disease, Tonsils Removed	
	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
Cultures of material from the throat														
Number studied	871	100.0	93	100.0	300	100.0	42	100.0	27	100.0	201	100.0	99	100.0
Negative	871	100.0	3	3.3	3	1.0	0	0.0	0	0.0	3	1.5	0	0.0
1 plus	0	0.0	20	21.5	4	1.3	1	2.4	2	7.4	3	1.5	1	1.0
2 plus	0	0.0	39	41.9	20	6.7	3	7.1	4	14.8	12	5.9	8	8.1
3 plus	0	0.0	13	14.0	29	9.7	6	14.3	4	14.8	20	9.9	9	9.1
4 plus	0	0.0	18	19.3	244	81.3	32	76.2	17	63.0	163	81.1	81	81.7
Cultures of material from the nose														
Number studied	825	100.0	56	100.0	289	100.0	39	100.0	25	100.0	193	100.0	96	100.0
Positive	0	0.0	11	19.6	190	65.7	19	48.7	19	76.0	122	63.2	68	70.9
Leukocyte count														
Number studied	53	100.0	20	100.0	299	100.0	42	100.0	27	100.0	201	100.0	98	100.0
Less than 9,000 per cu. mm.	25	47.2	13	65.0	69	23.1	14	33.3	5	18.5	43	21.4	26	26.5
9,100 to 12,900 per cu. mm.	23	43.4	6	30.0	83	27.8	11	26.2	6	22.2	53	26.4	30	30.6
13,000 to 15,900 per cu. mm.	5	9.4	1	5.0	67	22.4	12	28.6	6	22.2	49	24.4	18	18.7
16,000 per cu. mm. and over	0	0.0	0	0.0	80	26.7	5	11.9	10	37.0	56	27.8	24	24.5
Erythrocyte sedimentation rates (Westergren)														
Number studied	47	100.0	20	100.0	294	100.0	41	100.0	26	100.0	198	100.0	96	100.0
Less than 9 mm. per hour	17	36.1	12	60.0	26	8.8	6	14.6	4	15.4	19	9.6	7	7.3
9 to 19 mm. per hour	16	34.1	3	15.0	60	20.4	9	21.9	8	30.8	39	19.7	21	21.9
20 to 29 mm. per hour	6	12.8	4	20.0	61	20.7	14	34.1	4	15.4	43	21.7	18	18.7
30 to 39 mm. per hour	2	4.2	1	5.0	51	17.5	4	9.8	3	11.5	31	15.6	20	20.8
40 to 49 mm. per hour	3	6.4	0	0.0	39	13.3	3	7.3	5	19.2	24	12.1	15	15.6
50 mm. per hour and over	3	6.4	0	0.0	57	19.4	5	12.2	2	7.7	42	21.2	15	15.6

Headache (77.8 per cent), generalized aching (59.4 per cent) and chills (63 per cent) were the most common complaints. Forty-two and three-tenths per cent of the men coughed, but only 2.3 per cent did so severely. Hoarseness was notable by its rarity (1 per cent) in this group of patients.

Physical Signs.—Tonsillar and pharyngeal exudate has usually been regarded as the characteristic sign of streptococcic infection of the respiratory tract and was a prominent feature of the disease as observed during this study. It was present in small amounts in the throats of 18.3 per cent and in large amounts in 44 per cent of all patients. Much more notable is the fact that no exudate was seen for 37.7 per cent of these patients with proved hemolytic streptococcus infection.

Previous authors have described edema of the pharyngeal tissues in patients with streptococcic sore throats but have not sufficiently emphasized its frequency or its value as a diagnostic sign. Easily recognizable and characteristic swelling and edema of the tonsils, anterior and posterior pillars, soft palate and uvula were observed in 85.7 per cent of this group. Exudate was not present in many of these patients. Very often the encroachment of the engorged tissues on the faucial space was exceedingly great, and the airway itself was sometimes endangered. Lesser degrees of edema are, however, easily recognized by the inexperienced observer.

Most characteristic of all the pharyngeal signs of streptococcic infection was the abnormal redness of the palate, anterior pillars and other pharyngeal tissues, which was absent in only 3 per cent and present to an extreme degree in 83.6 per cent of all the patients. The fiery redness present in slightly more than half is unmistakable and very valuable in differential diagnosis. Considerable experience is, unfortunately, required in the interpretation of the lesser degrees of abnormality. It is important to note and distinguish between the various gradations of this sign since pronounced redness of the pharyngeal tissues may be observed in the absence of exudate or severe edema.

Tenderness of the anterior cervical glands was discovered to be the single most useful and reliable sign of infection of the throat by hemolytic streptococci since it is readily recognized and accurately interpreted by any physician. Tender glands were observed in 80.9 per cent and were very abnormal in 43.6 per cent of the patients in this group. The adenitis was usually bilateral, but only one side was affected in many instances. It is probably correct to state that more information could be obtained rapidly as to the frequency of streptococcic infection among a number of patients with acute infection of the respiratory tract by the palpation of the glands in the neck than by an examination of the throat.

Fever was noted during the hospital stay of nearly all of these patients, as was to be expected, since afebrile patients were not admitted. It is obvious that the height of the elevation of temperature cannot be used as a differential sign in the diagnosis of respiratory disease, but two points deserve emphasis. Men infected by streptococci were more noticeably febrile on the whole than were those men suffering from nonstreptococcic disease, but there were a considerable number of the former in whom only low grade fever was observed. Entirely afebrile patients with hemolytic streptococcus infection have been described elsewhere.[13]

Laboratory Studies.—The results of the study of the throat flora are of importance since hemolytic streptococci were present in very large numbers and as the predominant organism in 90.9 per cent and in moderate numbers in an additional 6.7 per cent of the patients in whom an antibody response was demonstrated. Very few or no hemolytic streptococci were discovered in the throats of 7 typical patients, in all of whom the causative agent was recovered from the nose. No explanation can be offered for this phenomenon other than that some technical errors inherent in swabbing the throat and in the preparation of cultures were made.

Cultures of material from the nose were made for nearly all these patients. Hemolytic streptococci were isolated in 65.7 per cent and were usually present in nearly pure culture. This procedure is of some value since inexperienced laboratory technicians are more likely to isolate and identify satisfactorily the causative agent in these circumstances. The culture of material from the nose is also much less likely to be positive in cases in which a "virus type" infection has occurred in a person who previously was a carrier of hemolytic streptococci.

The total leukocyte count was increased in 76.9 per cent of the cases of streptococcic infection but sufficiently so to be of diagnostic value (above 13,000 per cubic millimeter) in only 49.1 per cent. The erythrocyte sedimentation rate was accelerated in 91.3 per cent and was greater than 20 mm. per hour in 70.8 per cent of this group. Very often rates greater than 40 mm. per hour were recorded.

Effect of Tonsillectomy.—Bloomfield [7b] has previously stated that tonsillectomy confers a considerable degree of protection against infection of the respiratory tract by hemolytic streptococci. This was not the case in the group described in this report since the tonsils had been removed with equal frequency in men suffering from streptococcic infections and men with nonstreptococcic infections. Tonsillectomy had

13. Rantz, L. A.; Boisvert, P. J., and Spink, W. W.: Hemolytic Streptococcus Sore Throat: A Detailed Study of the Simultaneous Infection of a Large Number of Men by a Single Type, Arch. Int. Med. **76**:278 (Nov.-Dec.) 1945.

been performed on 33 per cent of the men in the former and 34.4 per cent of men in the latter group.

It is probable that the relationship between the presence of tonsils and streptococcic infection varies according to the types of strains of the organisms. More important is the striking effect of the absence of tonsils on the clinical manifestations of streptococcic infections of the respiratory tract. An inspection of columns six and seven of tables 1 and 2 shows that the symptoms of streptococcic infection in men with and men without tonsils are similar, as are the laboratory data, but the physical signs in the throat are different in the two groups. Exudate was demonstrated more frequently and in larger amounts in patients whose tonsils were intact; it was absent or present in minimal amounts in 80.8 per cent of the patients whose tonsils had been removed. The magnitude and the frequency of edema of the pharyngeal tissues were also less in the absence of tonsils, but the difference was not so striking.

Definite abnormal redness of the palate, anterior pillars and other pharyngeal tissues and tenderness of anterior cervical glands were the two manifestations of streptococcic infection observed as often in the absence as in the presence of tonsils. These signs are, therefore, of the greatest diagnostic importance.

Scarlet Fever.—A scarlatiniform rash was observed in 27 persons infected by hemolytic streptococci. The essential data obtained from these patients have been presented separately in column 5 of tables 1 and 2 for the purpose of emphasizing the essential similarity between patients with and those without rash. The tonsils had been removed from 15, or 55.5 per cent, of these men. When this fact is considered in relationship to the symptoms, the physical signs and the laboratory observations, it will be observed that the presence of a rash had no effect on the clinical nature of streptococcic infection of the respiratory tract. Somewhat higher temperatures were noted in association with a rash, but the differences in this respect between this group and the patients without rash were not great.

Atypical Streptococcic Disease.—It has been pointed out that the absence of tonsils greatly alters the physical signs of hemolytic streptococcus infection of the respiratory tract. A further elaboration of the problem of diagnosis of atypical infections is desirable. Exudate on the tonsils or tonsillar tags in association with other of the signs of streptococcic disease, described previously, and the demonstration of large numbers of group A hemolytic streptococci in the flora of the throat usually permitted the diagnosis of infection by these organisms. The problem was more difficult with the 37.7 per cent of all patients in whom exudate was not demonstrable. Edema, abnormal redness and adenitis assisted in the differentiation of three quarters of this group.

Nasopharyngeal signs were minimal in 33 men in whom an antistreptococcic antibody response occurred—a summary of the physical signs is presented in table 3. Tonsillectomy had been performed in 19, or 57.5 per cent.

The infections of 19 patients were properly classified principally on the basis of tender anterior cervical glands and the presence of large numbers of group A streptococci in the throat flora. Intense redness of the pharyngeal tissues of 5 patients was helpful. An additional 14 patients were considered, after the initial study, to have streptococcic infection, in spite of a paucity of signs which obviously did not allow accurate diagnosis in the absence of studies of antibody levels. Such patients will be further discussed in another section.

The principal feature to be emphasized is that febrile hemolytic streptococcus infection of the respiratory tract may occur in persons who exhibit only the most trivial abnormalities in the throat and that

TABLE 3.—*Physical Signs in Patients with Atypical Hemolytic Streptococcic Disease of the Respiratory Tract*

Number of Patients	Exudate	Edema	Redness	Adenitis	Tonsillectomy
4	0	0	0	0	3
3	0	0	0	1-2+	0
5	0	0	1+	0	3
3	0	1+	1+	0	2
4	0	0	1+	1-2+	3
7	0	1+	1+	1-2+	5
2	0	0	2+	0	0
5	0	0	2+	1-2+	3

tender glands will often be the critical sign in such patients. At least 5 to 10 per cent of all hemolytic streptococcus infections will be clinically indistinguishable from the "virus type" disease of the respiratory tract.

Composite Picture of Hemolytic Streptococcic Infection.—Hemolytic streptococcic infection of the respiratory tract, as observed during this study, was a febrile illness usually of acute onset and associated with the expected manifestations of such a disorder, including chills, headache, generalized aching and variable degrees of prostration. Many patients were excluded by the artificial method of selection, which required the presence of fever as an indication for hospitalization, and it must be constantly borne in mind that mild and inapparent infections are probably extremely common.

The characteristic symptom was sore throat, which was rarely absent and ordinarily severe. Cough and coryza were often present but were usually not prominent complaints. The rarity of hoarseness was notable.

Clinically typical hemolytic streptococcus sore throat was observed most frequently in men whose tonsils were intact and was characterized by varying amounts of tonsillar and pharyngeal exudate and varying

degrees of redness and edema of the pharyngeal tissues. In addition, tender anterior cervical glands were nearly always noted. It will be demonstrated later that the concatenation of these signs permits diagnosis of hemolytic streptococcus infection with a high degree of accuracy, even without a bacteriologic study of the flora of the throat.

A large number of patients remained, however, for whom the making of a diagnosis was more difficult since certain of these signs, particularly exudate, were absent. This was especially so if the tonsils had been removed. No difficulty arose if severe pharyngeal edema was observed in such patients, but there were approximately 10 per cent of the whole group with proved streptococcic infections in whom no or only minimal swelling of the throat could be discerned. In such persons tender glands in the neck, abnormal redness of the throat and large numbers of hemolytic streptococci in the nasopharyngeal flora permit a reasonably accurate differentiation from other types of infection of the respiratory tract. A certain number of adult patients with infections of the respiratory tract will always be discovered for whom a definite diagnosis cannot be made on clinical grounds, even though large numbers of group A hemolytic streptococci are recovered from the throat. The magnitude of this group will vary with the geographic area, the epidemic state of the community and the skill and the experience of the examining physician. Other aspects of this problem will be discussed later in the paper.

Moderate to large numbers of group A hemolytic streptococci were discovered in the throat flora of nearly all these patients with proved streptococcic infection. These organisms frequently appeared to be present in almost pure culture. Their absence in a few instances may possibly be explained on the basis of errors in the technics used in obtaining material for culture.

The total number of white blood cells and the erythrocyte sedimentation rate were usually increased in cases of hemolytic streptococcus sore throat, but both values were, unfortunately, often within normal limits in the cases presenting difficult problems in diagnosis.

NONSTREPTOCOCCIC INFECTION

Hemolytic streptococci were never isolated from the nasopharynges or throats of 871 patients with the symptoms and signs of disease of the respiratory tract. The infectious agents involved may well have been of a diverse nature but all such patients have been grouped together as having nonstreptococcic infections of the respiratory tract. The essential data obtained from these patients are presented in column 1 of tables 1 and 2.

This group of patients was very different clinically from those infected by hemolytic streptococci. The general symptoms of a febrile

illness were usually observed. Sore throat was, however, minimal or not present in the majority (66.3 per cent). Careful questioning often revealed that the pain on swallowing was caused by a disturbance, during this act, of an inflamed and tender larynx rather than by the edema of the pharyngeal tissues which is characteristic of streptococcic infection. Cough, which had not been a prominent feature of the symptom complex of the previous group, was present in 83.3 per cent and severe in 24.1 per cent. Definite hoarseness was noted in 13.1 per cent.

Great dissimilarity also existed between the physical signs of persons with streptococcic and those of persons with nonstreptococcic disease of the respiratory tract. Exudate was not detected in the throats of 95 per cent of the latter group. It was present in minimal amounts in 3.3 per cent but was not often associated with other abnormalities suggesting streptococcic infection, and was usually a thinner, more slimy material than that seen when hemolytic streptococci were the causative agents. There were 15 patients in whom large amounts of tonsillar exudate were observed but no hemolytic streptococci were discovered in the throat. Special comment will be made later on these patients.

Edema and abnormal redness of the nasopharyngeal tissues were minimal or not present in all but 10.9 per cent and 23.8 per cent, respectively, of all patients with nonstreptococcic disease of the respiratory tract. Adenitis was present in 13.6 per cent of these men but was severe in only 1.7 per cent.

The clinical laboratory investigation of this group of patients was incomplete, but it is clear that the total leukocyte count in cases of nonstreptococcic disease is rarely greater than 13,000 per cubic millimeter and that the erythrocyte sedimentation rate is usually less than in the previously described cases.

Patients with Atypical Infections.—Roughly 10 per cent of the total group with definite nonstreptococcic diseases presented signs suggesting infection by hemolytic streptococci. Most of these had noticeable edema and redness of the pharyngeal tissues, associated with tenderness of cervical glands. Such patients may be distinguished with certainty from other similar ones in whom streptococcic infection has occurred only if group A streptococci are not demonstrated to be present in the nasopharynx.

There were 15 patients with exudative tonsillitis in the study group in whom great edema and redness of the pharyngeal tissues and marked tenderness of cervical glands were also present. Repeated examinations failed to reveal hemolytic streptococci in the throat, and no antistreptococcic antibody response occurred in those in whom serial determinations were carried out.

In summarizing, 10 per cent of the patients with nonstreptococcic disease in whom exudate was not observed presented signs suggesting streptococcic infection. The infections of approximately 25 per cent of all patients in whom any amount of exudate was demonstrated and 10 per cent of those in whom exudate was present in large amounts were not of streptococcic origin.

Infection in Hemolytic Streptococcus Carriers.—Group A hemolytic streptococci were present in the throats of from 5 to 20 per cent of the healthy camp population. It was to have been expected, therefore, that these organisms would be demonstrated in the flora of the throats of a considerable number of men who were believed, on clinical grounds, to be suffering from "virus type" infection. This situation arose in 93 patients, 33 of whom harbored hemolytic streptococci in large numbers. The essential data from this group are presented in column 2 of tables 1 and 2. An inspection of this material shows that the disease of these patients resembled clinically the most typical examples of nonstreptococcic infection.

Exudate in only small amounts was present in 5 and slight tenderness of cervical glands in 12 patients. Large numbers of group A hemolytic streptococci were recovered from the throats of only 33.3 per cent of these men in contrast to 90 per cent of those proved to have been infected by these organisms. Serial antibody studies were carried out for 19 of these patients who harbored many hemolytic streptococci, and a response was demonstrated in only 2 of them. The separation of these men into a group was justified, although an error of 5 to 10 per cent was made.

The clinical resemblance of the disease of these patients to "virus type" infection was to be expected from the method of selection since the presence of hemolytic streptococci in the throat flora of a person presenting signs suggesting such infection naturally led to the classification of the infection as streptococcic. That errors were made during this process is obvious, because a group of patients has just been described in whom the physical signs of nonstreptococcic disease resembled closely those seen during streptococcic infection. Such a process occurring in a carrier of hemolytic streptococci would usually be believed to be an instance of infection by these organisms. These are, of course, included in the group classified as having hemolytic streptococcus disease of the respiratory tract without antibody response.

No method is available at present for differentiating the nonstreptococcic infection of the respiratory tract which occurs in a hemolytic streptococcus carrier with absolute certainty. The error will be small if both clinical and bacteriologic studies are undertaken. Ten per cent of nonstreptococcic infections resemble clinically those caused by streptococci. Ten to 20 per cent of them may occur in persons who

were previously carriers of hemolytic streptococci. One to 2 per cent of nonstreptococcic infections of the respiratory tract will, therefore, be believed erroneously to be instances of streptococcic disease.

Composite Picture of Nonstreptococcic Infection.—Nonstreptococcic disease of the respiratory tract as observed during this study was typically a disorder associated with cough and often with hoarseness. Physical examination usually revealed nearly normal nasopharyngeal tissues. Exudate, edema and abnormal redness were present to a minimal degree or were absent. Tender anterior cervical glands were rarely observed. A total leukocyte count of less than 13,000 per cubic millimeter and a normal or only moderately elevated erythrocyte sedimentation rate were observed. The characteristic features permitted the satisfactory identification of at least 90 per cent of all patients with nonstreptococcic infection. The others presented a more difficult problem.

Typical exudative tonsillitis occurred in a small number of men in the absence of nasopharyngeal hemolytic streptococci or of an antistreptococcic antibody response. In others edema, abnormal redness and adenitis with tenderness of the involved glands were discovered. If group A hemolytic streptococci were not recovered from the throat, these patients could be readily differentiated. Hemolytic streptococci were, however, often discovered in the nasopharyngeal flora of men with nonstreptococcic infection of the respiratory tract because these organisms were harbored in the throats of from 5 to 20 per cent of the various camp population groups.

When the "virus type" infection supervened in one of these carriers and presented typical clinical features, the diagnosis could be made with only small risk of error, particularly if hemolytic streptococci were present in small numbers. When the signs and symptoms were those usually seen in patients with streptococcic disease and hemolytic streptococci were isolated in relatively large numbers, a satisfactory differentiation could not be made. This situation has been shown to have prevailed in from 1 to 2 per cent of all instances of nonstreptococcic disease of the respiratory tract.

COMMENT

The clinical differentiation of streptococcic and nonstreptococcic diseases of the respiratory tract is not difficult when each occurs in its typical form. The contrast between the person to whom each swallow is agony, whose pharynx is red and edematous, whose tonsils are covered with exudate and whose cervical glands are large and tender and another who is hoarse and coughing and whose throat and neck are almost normal on physical examination is too striking to be missed by the most inexperienced physician. An error of only 10 per cent

was introduced in each group during the study just described if such characteristic infections were classified without bacteriologic study of the flora of the throat.

Considerable variation from these extreme cases may occur and still permit accurate separation into clinical groups, particularly if it be borne in mind that streptococcic infection may frequently occur without the formation of demonstrable exudate. A study of the throat flora will usually be necessary in these circumstances if maximal accuracy of diagnosis is to be attained. The recovery of large numbers of hemolytic streptococci from the nasopharynx of a person in whom moderate redness and edema of the pharyngeal tissues and tenderness of anterior cervical glands have been demonstrated makes imperative a diagnosis of hemolytic streptococcus infection.

There will remain a considerable number of patients suffering from infection of the respiratory tract who will be difficult to classify even after careful study of the throat flora. A few of these will have exudative tonsillitis of unknown cause. The more important portion will be composed of patients whose illness clinically resembles a "virus type" disease but in whom hemolytic streptococcus infection has occurred. It may be quite impossible to distinguish between certain of the latter group and those patients in whom a nonstreptococcic infection has supervened in a group A hemolytic streptococcus carrier. Reexamination of the patient and reinterpretation of the clinical laboratory data after the results of cultures of material from the throat are known may enhance the accuracy of classification.

Occasionally the presence of a scarlatiniform rash will be of value in differential diagnosis. The occurrence of such a rash is to be regarded only as an interesting manifestation of hemolytic streptococcus infection. Its presence does not indicate that the patient will be more severely ill, require more elaborate therapy or be more susceptible to suppurative and nonsuppurative complications than a person with a similar infection in whom a rash does not develop.[14]

No technics are available at present for the absolute differentiation of streptococcic and nonstreptococcic infection of the respiratory tract. The serial measurement of antistreptococcic antibodies will not accomplish this since an increas in these substances will not be demonstrable in a considerable number of patients with definite hemolytic streptococcus infection.

The problem presented by the approximately 5 per cent of all patients from whose throats hemolytic streptococci not of group A were isolated has not been considered in this discussion. About one

14. One of us (W. W. S.) feels that this statement is in part incorrect, since he believes that the severe forms of hemolytic streptococcus disease of the respiratory tract with rash should usually be treated with scarlet fever antitoxin.

third of these are believed to have been infected by members of groups C and G. The others were probably fortuitously present in the throats of persons with nonstreptococcic disease. The occasional discovery of these relatively less pathogenic streptococci in large numbers in the nasopharyngeal flora of patients suffering from disease of the respiratory tract may lead to confusion, since the ordinary clinical bacteriologic laboratory is not prepared to distinguish between the various serologic groups of hemolytic streptococci.

It is our opinion, based on the study described in this paper and on observations in civilian groups, that a differentiation between streptococcic and nonstreptococcic diseases of the respiratory tract in adults may be made in northern United States with an accuracy of approximately 70 per cent without bacteriologic study of the throat flora and in from 80 to 90 per cent if this laboratory procedure is included. The situation is probably different in the southern states, where streptococcic disease occurs infrequently. In these circumstances the atypical varieties of nonstreptococcic disease would be observed relatively more often and differential diagnosis would be correspondingly more difficult.

Satisfactory differential clinical diagnosis of acute nonpneumonic disease of the respiratory tract therefore requires information as to the nature of the infectious processes which occur commonly in a particular geographic area, experience in the interpretation of the abnormalities in the pharyngeal tissues and neck which may occur as the result of such infections and an adequate bacteriologic study of the nasopharyngeal flora.

MEGAKARYOCYTIC REACTION LOCALIZED IN THE BONE MARROW

Report of a New Hematologic Syndrome with Observations on the Origin and Development of Megakaryocytes and on the Derivation of Platelets

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HITHERTO there have been only two diseases known in which the megakaryocytes occupy the center of the pathologic picture. One is thrombopenic purpura, in which these cells suffer an injury. The other is chronic aleukemic myelosis, characterized by an extramedullary megakaryopoiesis. A case of acute megakaryoblastic leukemia, the only one so far recorded in the literature, was described by von Boros.[1] However, its authenticity is doubted by some hematologists.[2] In other lesions in which these bone marrow cells are involved, such as in chronic myeloid leukemia, hyperthyroidism and polycythemia, they merely play a secondary role.

In the present case the megakaryocytes were the elements affected principally and in a manner unique in hematologic history. It is reported, also, because of the light it throws on the problems concerning the origin and maturation of megakaryocytes and the derivation of platelets from them.

REPORT OF A CASE

G. M., a Filipino housewife, was admitted to the charity ward of San Juan de Dios Hospital on Oct. 14, 1940, complaining of headache and fever with general bodily weakness.

For about a year previous to the present illness she had been suffering from amenorrhea. More recently palpitation and precordial pain supervened which sometimes prevented her from continuing the day's work. Occasionally this precordial pain would become so severe that breathing was rendered difficult. Dizziness accompanied it now and then. For these complaints she did not seek any medical aid.

A week prior to the date of admission, she fell ill with severe cephalalgia, which she attributed to delayed meals and to baths at improper times. Three days later she had a chill followed by fever, which lasted till the ninth day of her

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1. von Boros, J.: Ueber einen Fall von akuter Megakaryoblastenleukämie, Ztschr. f. klin. Med. **118**:697, 1931.

2. (*a*) Stransky, E.: Personal communication to the author. (*b*) Forkner, C. E.: Leukemia and Allied Disorders, New York, The Macmillan Company, 1938, p. 184.

stay in the hospital. According to her, the chill occurred for only about a minute. Additional complaints were anorexia and general debility.

Physical Examination.—Physical examination on the day of entrance revealed very pale conjunctivas, eruptions at the right angle of the mouth and visible pulsation of the cervical vessels. Tactile fremitus was diminished on the right side over the infrascapular region. On the same area pulmonary resonance was impaired and vesicular breathing noticeably diminished. A faint systolic murmur was heard over all the valvular areas except over the tricuspid valve. There were no other abnormal pulmonary and cardiac observations. Lymph nodes were not enlarged. The liver and spleen were not palpable. There were no petechial hemorrhages, no jaundice and no pain over the bones and joints. The blood pressure was 100 systolic and 65 diastolic, the temperature 38.8 C. (101.8 F.), the radial pulse rate 98 beats per minute and the respiration rate 30 per minute. There were no complaints involving other systems.

Past History.—The past history disclosed an attack of influenza and another disease simulating acute rheumatic fever. She had not suffered from any appreciable loss of blood, and had never been hospitalized before.

Résumé of Laboratory Examinations.—During her forty-four day sojourn in the hospital, five routine examinations of the urine, eight of the blood and seven of the feces were made. In the first four urinary examinations (made on October 19, 24 and 29 and November 5) albumin in moderate amount, with granular casts (1 plus) and hyaline casts (1 plus) was detected. Pus cells (4 plus) and erythrocytes (1 to 3 plus) were also encountered. The fifth examination (November 28) showed normal urine. The specific gravity in all examinations was consistently within the normal range.

All examinations of the feces disclosed ova of Trichuris trichiura and of Ascaris lumbricoides. No ova of Ankylostoma were seen.

Four examinations for occult blood in the stools gave negative results.

The first examination of the blood (October 18) showed a hemoglobin content of 60 per cent (Tallqvist), 2,675,000 red cells per cubic millimeter and 16,200 white cells. The differential count was as follows: 80 per cent polymorphonuclear leukocytes, 18 per cent lymphocytes and 2 per cent monocytes.

In subsequent examinations, the hemoglobin values oscillated between 55 and 70 per cent, the red blood cells between 2,950,000 and 3,380,000 and the white blood cells between 25,500 and 4,250 per cubic millimeter; the polymorphonuclears oscillated between 81 and 60 per cent, the lymphocytes between 17 and 38 per cent, the monocytes between 1 and 3 per cent and the eosinophils between 0 and 2 per cent.

Platelets were counted four times, the number ranging from 200,000 to 290,000 per cubic millimeter.

Serologic examination yielded an icterus index of 2 and a Widal reaction positive up to a dilution of 1:320 (2 plus). Culture for Bacillus typhosus was negative.

Roentgenographic examination of the skull and sternum showed no pathologic changes of the bone.

Temperature Curve.—During the first eight days of hospitalization the patient had a remittent fever. The chart showed four peaks occurring on the second (39.9 C. [103.8 F.], sixth (39.8 C. [103.6 F.], seventh 39.8 C. [103.6 F.]) and eighth (39.5 C. or 103.1 F.) days. Between peaks the temperature dropped slightly but did not touch normal. On the ninth day the fever disappeared, and throughout the rest of her sojourn she remained afebrile, except for an occasional slight 0.1 to 0.4 degree [C.] rise of temperature above the normal occurring, at noon.

Treatment.—Santonin and a purgative were routinely administered on the first day and quinine and methenamine during fever. Later the patient was given iron and ammonium citrates, in doses of 6 Gm. daily, till her discharge.

Comment.—Although the Widal test yielded a positive result, the diagnosis of typhoid was rejected by the attending physician on account of the inconsistent clinical observations and the results of the examination of the blood. Pyelitis was the diagnosis given for the febrile condition.

The remainder of the patient's days in the hospital were given to the treatment of her anemia. However, the red blood cells did not increase beyond 3,380,000 per cubic millimeter. This unexplained anemia is the theme of this report.

Follow-Up.—Six months after the patient's discharge from the hospital (May 28, 1941) I examined her. She was still pale and complained of weakness. However, she was able to carry on her usual household duties. She was pregnant at the time. The lungs and heart were apparently normal, and the spleen and liver were not palpable. No pains were felt over the bones. No recurrence of the febrile ailment for which she had been hospitalized before existed. Specimens of peripheral blood were secured for various examinations. She refused to permit a sternal puncture at this time.

HEMATOLOGIC PICTURE

In connection with my studies of the blood, I secured a specimen of the sternal marrow. The unexpected presence of numerous megakaryocytes in the smear led me to make a more detailed study of the case. My examinations gave the following results, arranged in chronologic order:

On Oct. 20, 1940 the patient's temperature was 38.4 C. (101.1 F.). A cell count of bone marrow from the manubrium of the sternum showed 596,000 nucleated cells per cubic millimeter with the following differential distribution: myeloblasts, 5.4 per cent; premyelocytes, 17 per cent; basophils, 1.4 per cent; eosinophils, 8.2 per cent (myelocytes, 1.7 per cent; juvenile form, 2.5 per cent; stab forms 0.9 per cent, and segmented forms, 3.1 per cent); neutrophils, 63.5 per cent (myelocytes, 14.9 per cent; juvenile forms, 20.7 per cent; stab forms, 17.5 per cent, and segmented forms, 10.4 per cent); lymphocytes, 3.5 per cent; monocytes, none, and mitotic white blood cells, 1 per cent. There were 164 nucleated red cells counted for every 350 white cells. Of the former 12 were proerythroblasts, 21 basophilic erythroblasts, 13 macroblasts, 105 normoblasts, 8 mitotic red cells and 5 megaloblasts. The myeloid-erythroid ratio was 2.1:1. There were 4,000 megakaryocytes counted for every 1,000,000 nucleated bone marrow cells. No specimen of the peripheral blood was taken on this day.

On Oct. 22, the patient's temperature was normal. The Schilling hemogram was: basophils, 0.4 per cent; eosinophils, 1.4; myelocytes, 1.6 per cent; juvenile forms, 1.6 per cent; stab forms, 30.8 per cent; segmented forms 47.2 per cent; lymphocytes, 13.8 per cent, and monocytes, 3.2 per cent. There was 1 normoblast for every 250 white blood cells. Moderate anisocytosis and poikilocytosis and pronounced rouleaux formation were noted. Many of the lymphocytes showed more basophilic cytoplasm than ordinarily observed; their nuclei displayed tendency to blocking. Vacuoles were observed in the cytoplasm of the monocytes. No unusual features were noted in the granulocytes. Platelets were numerous and of three varieties (to be described later). No megakaryocytes were found. The reticulocyte count was 15 for every 1,000 red blood cells.

On October 30, although the liver and spleen were not enlarged, attempts were made to puncture them. The attempt on the latter failed. Examination of the material secured from the liver yielded nothing significant.

On November 2 the patient's temperature was normal. Bone marrow from the sternum contained 595,000 nucleated cells per cubic millimeter. The differential count was as follows: myeloblasts, 4.8 per cent; premyelocytes, 11.6 per cent; basophils, 0.4 per cent; eosinophils, 2.4 per cent (myelocytes, 1.2 per cent; juvenile forms, 0.8 per cent; stab forms, 0 per cent, and segmented forms, 0.4 per cent); neutrophils, 74.4 per cent (myelocytes, 19.6 per cent; juvenile forms, 24.8 per cent; stab forms, 26.4 per cent, and segmented forms, 3.6 per cent); lymphocytes, 3.6 per cent; monocytes, 1.2 per cent, and mitotic white blood cells, 1.6 per cent. Two plasma cells were counted for every 250 white blood cells. Eighty-six nucleated red blood cells were counted for every 250 white blood cells. Of the nucleated red blood cells, 6 were proerythroblasts, 2 basophilic erythroblasts, 5 macroblasts, 69 normoblasts, 3 mitotic red blood cells, and 1 megaloblast. The myeloid-erythroid ratio was 2.9:1. Two thousand, five hundred and fifty-eight megakaryocytes were counted for every 1,000,000 nucleated marrow cells.

On November 11, the patient's temperature was normal. The Schilling hemogram was: basophils, 1.2 per cent; eosinophils, 0.8 per cent; myelocytes, 0.8 per cent; juvenile forms, 1.6 per cent; stab forms, 23.2 per cent, and segmented cells, 33.6 per cent; lymphocytes 36.4 per cent; plasma cells, 0.4 per cent, and monocytes, 2.0 per cent. Platelets were still numerous. The condition of the red blood cells was practically the same as that on October 22. No megakaryocytes were found.

On November 12 the Wintrobe values were as follows: hemoglobin (Dare), 6.37 Gm. per hundred cubic centimeters of blood; red cells, 3,800,000 per cubic millimeter; volume of packed cells, 21.8 cc. per hundred cubic centimeters of blood; mean cell volume, 57 cubic microns, and mean cell hemoglobin, 16.7 micromicrograms.

Follow-up study on May 28, 1941, yielded the following results: The hemoglobin was 50 per cent (Tallqvist); red cell count was 3,455,000 per cubic millimeter, and white cell count was 7,850 per cubic millimeter. There were between 185,000 (Rees-Ecker) and 186,570 (Fonio) platelets per cubic millimeter. The coagulation time was six and one-half minutes (Lee and White). The icterus index was 3.1 units. The bleeding time was two and one-half minutes (Duke). Clot retraction was normal.

The Schilling hemogram was: basophils, 0 per cent; eosinophils, 4 per cent; myelocytes, 0 per cent; juvenile forms, 0 per cent; stab forms, 12 per cent; segmented forms, 33 per cent; lymphocytes, 48 per cent, and monocytes, 3 per cent. Platelets were not as numerous as before, but the same three varieties existed among them. No megakaryocytes were found.

Comment: A 14 B. D. special needle was used for the sternal puncture. Less than 0.5 cc. of bone marrow was secured each time. The cell count was made by placing a drop of the material on a slide with the ordinary white cell pipe. Direct smears were made on several slides and stained with Wright and Giemsa solutions. The nomenclature of the cells used here is that of Stransky and Quintos.[3]

The counting of the megakaryocytes was done directly on the stained smear. Several millions of the nucleated marrow cells were counted, with the correspond-

3. Stransky, E., and Quintos, F. N.: The Diagnostic Value of Examination of Sternal Marrow, Acta med. Philippina **2**:217, 1940.

ing megakaryocytes. Then the average per million was taken. This is conveniently done under the high power objective, with the lower lens of the eyepiece divided into several portions by thinly drawn ink lines.

DESCRIPTION OF CELLS

The two interesting features associated with the present case are the atypical forms of platelets found in the peripheral blood and the superabundance of megakaryocytes in the bone marrow. These are the blood elements to be described.

Peripheral Blood.—The platelets may be grouped into three varieties. The first series consists of platelets occurring singly, or in groups and in chains of two, three or more. They correspond to the normal platelets described by Jürgens and Graupner[4] (fig. 5 *B 1*). Some are old, with brilliant refractile granules, while others are a little younger.

The second variety (fig. 5 *B 2*) consists of big clumps of protoplasm detached from promegakaryocytes. Unless closely examined, they may be mistaken for mere clusters of mature platelets. Minute scrutiny, however, reveals that while the chromomeres are fully formed the cytoplasm has not yet fragmented itself into hyalomeres. This condition interferes with an accurate enumeration of platelets. To avoid confusion the members of the laboratory staff and I have excluded them in our respective counts. These fragments are like indiscriminately torn pieces of paper, assuming all sorts of shapes. Their structure tallies with the description of the pathologic irritative forms of platelet by Jürgens and Graupner. They are frequently found in primary polycythemia and are beautifully illustrated in figure 8 accompanying the cited article of these writers.

The third variety is composed of protoplasmic shreds broken off from old megakaryocytes. They do not show any tendency to divide into platelets. Rather, they appear to be on their way to dissolution. They stain lilac, without any trace of blue, and are studded with azurophilic granules which are much finer than, and are not disposed in heaps as, those found in the chromomeres of normal platelets. Compare figure 5 *B 3* with the cytoplasm of the megakaryocyte in figure 4 *B*. Their similarity in structure points to a probable derivation of one from the other.

No vacuoles are found in any type.

The atypical forms observed by Downey and Nordland,[5] and Carpenter and Flory[6] in cases of chronic aleukemic myelosis were not encountered.

4. Jürgens, R., and Graupner, H.: Darstellung eines Entwicklungssystems der Thrombocyten, Folia haemat. **57**:263, 1937.

(Footnotes continued on next page)

Bone Marrow.—The sternal marrow is hyperplastic in all its elements. However, the megakaryocytes appear to have outpaced the leukocytes and the red blood cells. This is evident from the count of all nucleated cells, as well as from the stained smear (fig. 1.). This disproportionate megakaryopoiesis is the interesting feature for the present. All stages of development are represented and lend to a more detailed study of this blood element.

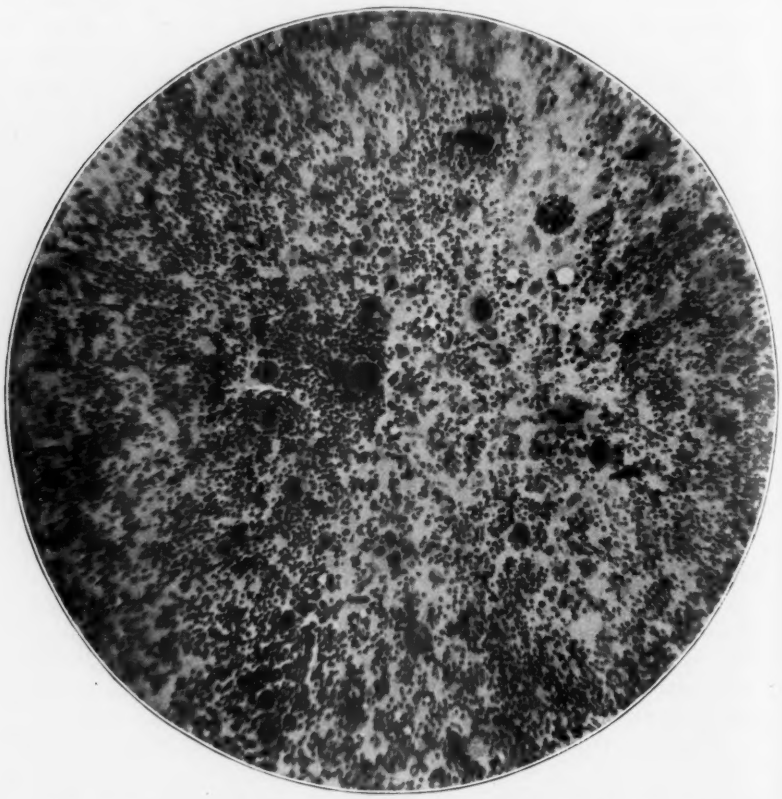

Fig. 1.—Bone-marrow smear under the low power objective, showing numerous megakaryocytes (photomicrograph by Dr. Medina-Cué).

The nomenclature, classification and criterion of maturity are still confusing. This is rather unavoidable because the nucleus and cytoplasm

5. Downey, H., and Nordland, M.: Hematologic and Histologic Study of a Case of Myeloid Megakaryocytic Hepato-Splenomegaly, Folia haemat. **62**:1, 1939.

6. Carpenter, G., and Flory, C. M.: Chronic Nonleukemia Myelosis, Arch. Int. Med. **67**:489 (March) 1941.

of the megakaryocyte do not mature concurrently as in the granulocyte. This dissociation in growth has already been observed by Barta,[7] and it constitutes an essential difference in the maturation of this cell from maturation in other blood elements.

Hence, in selecting an adequate measure of the age of a given megakaryocyte, it is necessary to choose between the nucleus and the cytoplasm. Limarzi and Schleicher[8] have taken "the amount, character and arrangement of azurophilic granules in the cytoplasm" as the better criterion.

The "megakaryoblast-promegakaryocyte-megakaryocyte" classification is adopted in this report since this is more universally accepted than any other.

Megakaryoblast.—This is the youngest cell of the series (fig. 2 *A, B, C, D and E*). Its contour is round or oval. The nucleus occupies a greater portion of the cell than it would in a myeloblast and is centrally located. It stains more deeply lavender than that of a myeloblast, and it stands out clearly from the cytoplasm. The chromatin threads are sharply defined, disposed in reticulate pattern and separated from one another by intervening achromatic rounded spaces. The nucleus is round (fig. 2 *E*), oval (fig. 2 *A*) or kidney-like (fig. 2 *B*), depending on the degree of maturity. No nucleoli are present.

The cytoplasm is scanty and stains a deep blue. It does not contain granules. The spongioplasm is usually more abundant in the periphery. In the very early stage it is homogeneously basophilic, and as the reaction of both nucleus and cytoplasm to the stain, as has already been observed by Medlar,[9] is of the same degree of intensity, the contrast between them in the ordinary black and white photograph is considerably lessened, enough to make the delimitation of the nuclear margin difficult.

In the less immature forms, the spongioplasm is more abundant in the periphery than in the perinuclear zone.

Promegakaryocyte.—This stage (figs. 3 *A, B, C* and *D*, 4 *A*, and 5 *A*) presents the greatest number of variations in size, shape and character of both nucleus and cytoplasm. Generally the cell increases in size, the cytoplasm much more rapidly than the nucleus. The latter moves to an excentric position and becomes lobulated. The chromatin strands grow coarser and stain deeper. The interstices between strands

7. Barta, I.: Ueber Bau und Funktion der Megakaryozyten, Folia haemat. **47**:168, 1932.

8. Limarzi, L. R., and Schleicher, E. M.: The Reaction of Peripheral Blood and Bone Marrow in Chronic Hemorrhage and in Essential Thrombopenic Purpura, J. A. M. A. **114**:12 (Jan. 6) 1940.

9. Medlar, E. M.: A Study of the Megakaryocyte in the Circulating Blood of Rabbits Inoculated with Benzol and with Saponin, Folia haemat. **53**:397, 1935.

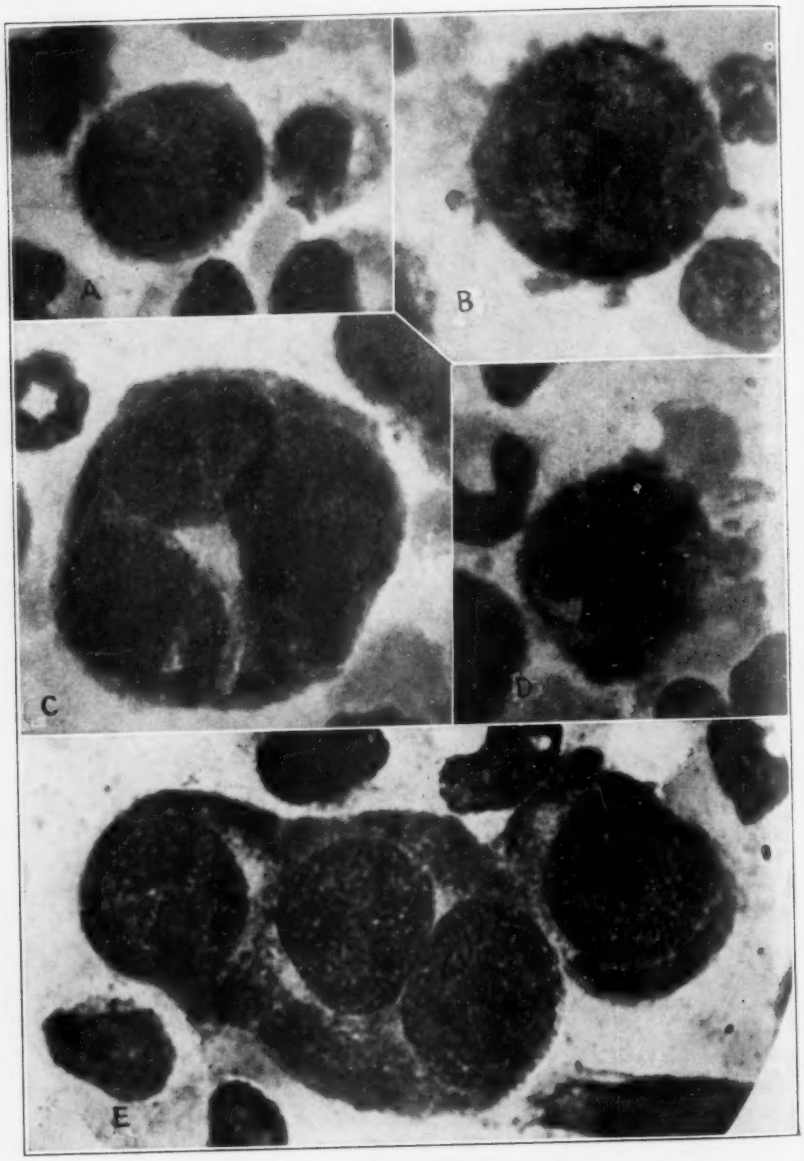

Figure 2

(See legend on opposite page)

are greatly widened. Thus, in a later stage the nucleus presents a miniature picture of a heap of noodles.

The dark blue cytoplasm becomes paler in parts as lilac refractile granules, distributed either singly or in brilliant clusters, appear near the nucleus or scattered throughout the altered cytoplasm. Pseudopodia may protrude which either are homogeneously basophilic or contain granules at the center.

The conflicting descriptions of this cell by various authors are explained by the different criteria of maturity employed.

For the sake of clearness and distinctness I have taken as the specific trait of this stage a cytoplasm that is partly basophilic and partly granular; this contrasts with the purely basophilic cytoplasm of the megakaryoblast and with the purely granular cytoplasm of the adult megakaryocyte.

The cell in fig. 3 *A*, has just emerged from the megakaryoblastic stage. The portion of the cytoplasm in the left upper quadrant has grown paler and shows granules. In fig. 3 *B*, the zone of diminishing basophilia is wider and contains more granules. In some cases, the cytoplasm presents an outer, homogeneous and an inner, granular region. As maturation progresses, the homogeneous area recedes outward till it forms a mere rim around the cell (fig. 4 *A*).

Frequently the nucleus and the adjacent granular cytoplasm are overstained (fig. 5 *A*) so that they appear as a single area, an error which gave Willi [10] the impression that platelets may originate from the nucleus. Closer examination, however, reveals clearly the separation between the nucleus and the surrounding granular area. This cell offers a photographic difficulty, because it presents three different focal planes. The marginal slightly basophilic and homogenous zone is indistinctly seen in the picture; to bring it out, its outline is indicated by arrows. It sends out pseudopodia. The inner perinuclear region

10. Willi, H.: Ueber den Bau und die Funktion der Megakaryocyten und ihre Beziehungen zur thrombopenischen Purpura, Folia haemat. **53**:426, 1935.

EXPLANATION OF PLATE.

Fig. 2.—Megakaryoblasts in different stages of amitosis. *A* (longest diameter 13.1 microns), showing at about the 11 o'clock position of the nucleus a V-shaped area with a transparent apex, the first sign of nuclear division; *B* (longest diameter 17.5 microns), a more advanced stage in which the line of cleavage and indentations of the nucleus at opposite poles are visible. The cell exhibits pseudopodia. *C* (longest diameter 23.75 microns), one nucleus (the vacuole in it is an artefact) has already separated from the mother-nucleus, while three others are being formed; *D* (longest diameter 15.25 microns), a megakaryoblast with three nuclei (slightly out of focus); *E* (longest diameter 21.35 microns), at the right, a daughter megakaryoblast is about to be separated, and at the left, the transparent zone between the two nuclei becomes basophilic preliminary to final separation (photomicrograph by Dr. A. Legarda).

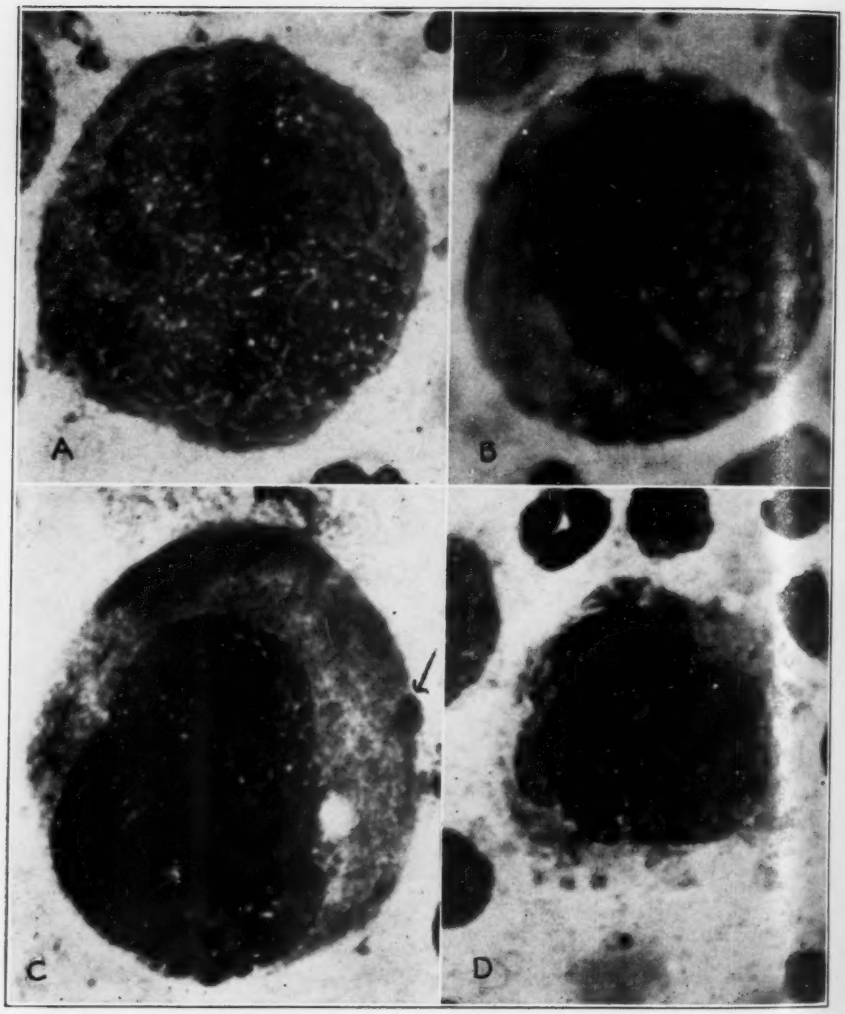

Fig. 3.—Promegakaryocytes at various stages of maturity. *A* (longest diameter 27.5 microns), cytoplasm at 10 o'clock becomes less basophilic, with clusters of granules at several places and the nucleus is indented at four points; *B* (longest diameter 25.2 microns), a more advanced stage; *C* (longest diameter 33.75 microns), darkest portion of the cytoplasm indicates basophilia, and arrow points at ingested object; *D* (longest diameter 22.5 microns), remnant of cytoplasm with mature nucleus after detachment of platelets, portions of remaining cytoplasm still basophilic and nongranular, while the rest is already forming platelets (photomicrograph by Dr. A. Legarda).

Fig. 4.—*A*, promegakaryocyte (longest diameter 43.75 microns), showing a narrow blue nongranular rim, granules of the finer type not in clusters but more or less evenly scattered and a phagocytosed body; a pearl-shaped vacuole (not a nucleolus) is at the upper part of the nucleus (photomicrograph by Dr. A. Legarda); *B*, a very mature megakaryocyte (longest diameter 69.5 microns), with transparent cytoplasm studded evenly with fine granules and containing two small pieces of ingested material (photomicrograph by Dr. Medina-Cué).

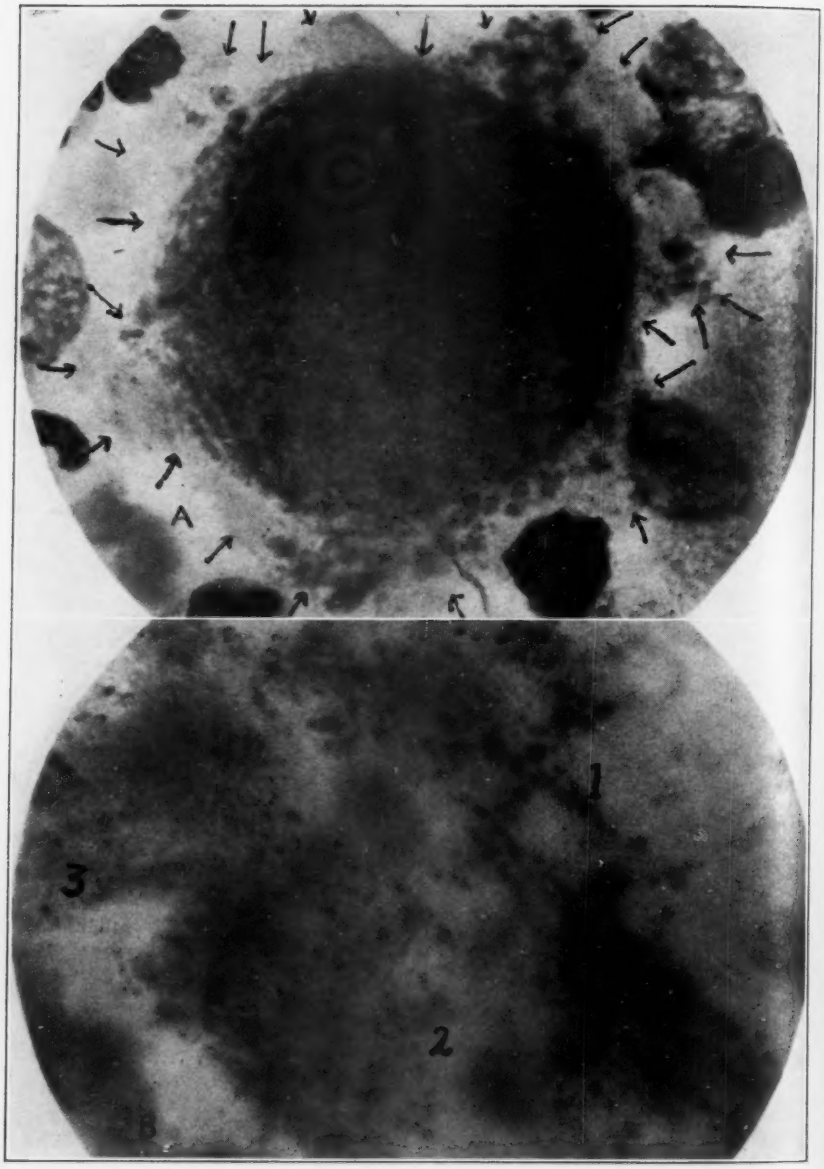

Fig. 5.—*A*, promegakaryocyte (longest diameter 43.75 microns) producing platelets; arrows indicate the wavy margin of the cytoplasm, which is divided into a peripheral slightly basophilic nongranular zone and a perinuclear granular zone; *B*, smear of peripheral blood showing three forms of platelets: (1) normal platelet, (2) pathologic irritative platelet and (3) a fragment of the cytoplasm of the kind of adult megakaryocyte shown in figure 4, *B* (photomicrograph by Dr. A. Legarda).

is a sheet of platelets in formation. The nucleus has reached its maturity, presenting a honeycombed pattern.

At times, two round or oval nuclei at opposite poles may be seen. Examples of phagocytosis and of platelet formation are observed in great number.

A promegakaryocyte may occasionally be as small as a megakaryoblast, but the nucleus is much coarser and at times is lobulated, while the cytoplasm is already well advanced in the process of fragmentation into platelets.

Adult Megakaryocyte.—This is the biggest cell of the series and marks the final stage in its development. The cytoplasm is enormous; it is uniformly granular, and it stains pale violet-pink, with or without a bluish background. The lilac granules are of two sizes. The bigger ones are arranged in clusters similar in appearance to those of the platelets; the finer ones are distributed more or less evenly throughout the cytoplasm. When granules are of the latter type, the cytoplasm loses all tinge of blue, becomes diaphanous and gradually thins out toward the periphery until one is at a loss to determine the extent of the margin and whether the dustlike particles at the outermost part are still connected with, or merely gathered around, the cell (fig. 4 *B*).

The lobulated nucleus recoils on itself in such a way that the opposite poles either meet or overlap one another. The chromatin materials are twined into thick threads which run in all directions, appearing like a network haphazardly woven. Oval or ellipsoid aggregates mark the crossing of the strands of chromatin.

Degenerated Forms.—This group comprises cells with torn or cytolized cytoplasm and bare or pyknotic nuclei. A percentage determination of the different types made from the first smear is as follows: megakaryoblasts (including amitotic forms) 13.5 per cent, promegakaryocytes 16.0 per cent, megakaryocytes 51.5 per cent and degenerated forms 19.0 per cent.

The pathologic forms observed by Downey and Nordland [5] in their case of chronic nonleukemic myelosis and by Limarzi and Schleicher [8] in thrombopenic purpura are not found in the smear.

Observations: It will be noted in the preceding description that for each type of cytoplasm there is a corresponding nucleus. However, unlike that in the granulocyte, the range of variation in character, size and shape of the cytoplasm of the megakaryocyte is much narrower and more definite than in its nucleus. For instance, the nucleus of the cell in figure 5 *A* has reached its maturity, but it may be found in a cytoplasm that is still immature or has already matured. This speaks for the suitability and propriety of taking the cytoplasm as the primary criterion of maturity of cells in the megakaryocytic series. Besides, the changes of the cytoplasm are more sharply defined than those

of the nucleus, thus facilitating the classification of a given cell by even a less experienced examiner.

Comment: This is a case of simple hyperplasia of the bone marrow of unknown origin, involving all the three blood elements. The granulocytes and the nucleated red blood cells increase at an equal rate, as revealed by the preservation of the normal myeloid-erythroid ratio, while the third blood element outnumbers both, as shown by the disturbance in the normal ratio between megakaryocytes and the rest of the nucleated bone marrow cells. The normal ratio, as determined by Limarzi and Schleicher,[8] is 58.8 megakaryocytes for every 1,000,000 nucleated cells in the bone marrow.

The differential counts of both white blood cells and nucleated red blood cells are within the physiologic range.

There is no evidence of replacement of one type, or types, of cell by another in the bone marrow nor of the existence of myeloid metaplasia, since the liver and spleen are practically normal.

This hyperplasia of the central hemopoietic organ is not reflected in the peripheral blood, except in the case of the platelets, as previously noted. Abnormal cells, other than a few normoblasts, have not been observed. On the contrary, the red blood cell count and the hemoglobin content are below normal. The anemia is microcytic and hypochromic. The coagulation and bleeding times, the retractility of the clot and the icterus index are within the normal limits.

Clinically, the patient, except for an episode of fever, presents no complaints besides anemia and the symptoms and physical observations consequent on its existence.

In view of the peripheral blood picture, iron deficiency may suggest itself, but the bone marrow does not show any abnormal increase of the normoblasts or a disturbance of the myeloid-erythroid ratio in favor of the latter, which are among the usual changes in iron deficiency anemia.

A bone marrow picture of this type has not yet been mentioned in medical literature.

The history of the patient does not offer any datum which one may correlate with the origin of this obscure anemia. Only the persistence of a slight shift to the left in the peripheral blood may lead one to suspect the presence of a low grade chronic infection. It is unfortunate that no roentgenogram of the lungs was taken in view of the abnormal pulmonary conditions detected during the patient's hospitalization. However, these abnormal signs disappeared and were not found in an examination I made six months later.

Apart from this, there is nothing more that could be gathered to furnish any clue to the explanation of this case.

ORIGIN AND DEVELOPMENT OF MEGAKARYOCYTES AND PLATELETS

Besides the clinical and hematologic puzzle with which this case confounds the diagnostician and the nosologist, the numerous normal megakaryocytes present an excellent opportunity for a detailed study of their origin, development and termination.

Frey [11] has summarized most of what was known on this subject up to 1928; reference should be made to his article by students interested in the matter.

Several views have been propounded on the origin of the megakaryocyte. Askanazy [12] expressed the belief that it was developed from endothelial cells, leukocytes and reticular cells; Naegeli [13] suggested the myeloblast as its probable origin and others, like Medlar,[9] postulated the fusion of histioid elements. On the other hand, Rothermel [14] concluded from her studies on the spleen of the normal cat, "that the megakaryocyte may therefore probably be interpreted as belonging to the group of cells of the erythrocyte series." In our case, Naegeli's theory is clearly borne out. In the words of Downey, Palmer and Powell,[15] whose published observations are in agreement with those of Naegeli, "the nuclei . . . usually take the primary step towards differentiation by simple increase in size or by an amitotic division."

The transformation from myeloblast begins with the simultaneous occurrence of four events, namely, the appearance of a clear transparent zone in the nucleus near the margin or at any point on the destined line of cleavage, a thickening of the chromatin strands, an increase in the basophilia of the cytoplasm, and an enlargement of the cell as a whole. The cell in figure *2 A* shows at the left upper quadrant of its nucleus a V-shaped area (distinctly seen under the microscope) with a transparent apex. This transparent point then lengthens into a line (fig. *2 B*), at both ends of which the nucleus becomes indented. At the same time, the chromatin strands thicken and grow denser and the cell itself increases in size. Figure *2 C* shows one new nucleus which has separated from the original nucleus, while three others are in process of formation. The transparent zone,

11. Frey, H. C.: Das Verhalten der Megakaryozyten im menschlichen Knochenmark und deren Beziehungen zum Gesamtorganismus, Frankfurt. Ztschr. f. Path. **36**:419, 1928.

12. Askanazy, M., cited by Frey.[11]

13. Naegeli, O.: Blutkrankheiten und Blutdiagnostik, ed. 4, Berlin, Julius Springer, 1923.

14. Rothermel, J. E.: A Note on the Megakaryocytes of the Normal Cat's Spleen, Anat. Rec. **47**:251, 1930.

15. Downey, H.; Palmer, M., and Powell, L.: The Origin of the Megakaryocytes in the Spleen and Liver in a Case of Atypical Myelosis, Folia haemat. **41**:55, 1930.

previously mentioned, appears to be part of the cytoplasm seen through the cleft created by the dividing nucleus. Medlar's statement that the presence of odd numbers of nuclei (fig. *2D*) militates against the theory of Naegeli receives support only if the division is mitotic.

As soon as the new nuclei are formed, the cytoplasm adjusts its shape for the termination of the process. It lengthens, and the transparent area acquires the basophilic character of the rest of the cytoplasm. Then the latter constricts and each nucleus is furnished with its own cytoplasm. Thus a new megakaryoblast is generated.

A few important facts necessary for a clearer understanding of the physiologic and pathologic variations in the development of the megakaryocyte follow.

The nucleus of the megakaryocyte which initiates the process of multiplication retains and displays its tendency to divide in all phases of maturation. It develops so rapidly that the cytoplasm cannot keep pace with it.

The cytoplasm, on the other hand, matures in such a way as to render it fit for the performance of its functions, namely the formation of platelets and phagocytosis. This begins at the promegakaryocytic stage, i. e., as soon as basophilia diminishes and granules appear. At the same time its capacity to follow the nucleus in dividing disappears.

It seems as if there is a fundamental conflict of some sort in the purposes of the nucleus and of the cytoplasm which underlies the observed dissociation in their respective growths. The nucleus engages in the generation of as many new cells as possible before the cytoplasm commences its proper functions; the cytoplasm, on the contrary, is inactivated during the phase of nuclear activity, for as long as multiplication continues it cannot form platelets or phagocytose foreign materials.

This should not lead one rashly to conclude that amitosis, not mitosis, is normally the commoner mode of multiplication of megakaryocytes, since it adequately actualizes the nuclear tendency; an alternative hypothesis is that, mitosis being normally the commoner, amitosis is imposed on the cell by an abnormal stimulus to rapid multiplication. So far there is no evidence to establish conclusively one theory or the other. The statement of Downey, Palmer and Powell,[15] "Although the occurrence of mitosis of the nuclei has been noted, this exists only in the more mature cells and is not a means of nuclear extension in the younger forms," was inferred from their observation of a case of atypical myelosis, an abnormal condition. My observation of the present case, however, tallies with theirs, for I have seen only one mitotic form in the bone marrow smear, and this is in the promegakaryocytic phase.

Now, as the megakaryoblast becomes a promegakaryocyte, the cytoplasm undergoes the alterations previously described. The emergence of granules is preceded by a diminution in the basophilia of that region in the cytoplasm where they occur. The bigger granules which are arranged in brilliant clusters are undoubtedly the precursors of the chromomeres of platelets. This area of diminishing basophilia may appear in any portion of the cytoplasm; however, it is usually first noted near the nucleus. As it widens, platelets are formed and detached, so that in the smear cells may be seen with scanty cytoplasm which is partly still basophilic and nongranular and partly forming platelets (fig. 3 *D*).

The cytoplasm which exhibits the finer and evenly distributed granules (fig. 4 *A* and *B*) is more concerned with phagocytosis than with the formation of platelets. Phagocytosed materials may be observed in the cytoplasm. At times, the same cytoplasm may be seen performing both functions, but it is not unlikely that only a few platelets will be formed, while the rest will be engaged in phagocytosis (fig. 3 *C*).

When the cytoplasm is converted into platelets it commonly does not reach the adult stage of development intact. This is the reason for not encountering frequently a fully matured megakaryocyte forming platelets. The term "fully matured megakaryocyte," as here used, designates any megakaryocyte no portion of whose cytoplasm is in a nongranular form.

On the other hand, when the cytoplasm is destined for phagocytosis, it loses entirely its basophilic character. In the stained smear, it appears purely lilac in color. The granules become finer and dustlike in size and shape and are distributed evenly. The cytoplasm itself grows more and more transparent, till it appears merely as a thin aggregate of dustlike particles (fig. 4 *B*). Finally, it disappears by dissolution, leaving the nucleus bare.

The maturation of the nucleus is characterized by the thickening of the chromatin threads, the deepening of their reaction with the stain, the widening of the interstices between them and the continued formation of lobes. In the final stage, its internal structure recalls a cross section of the mastoid bone. What distinguishes the behavior of the megakaryocytic from the granulocytic nucleus is its tendency to recoil on itself. It appears to me that such lobe formation, in contrast with the segment formation of neutrophils, is an expression of aborted amitosis. Such an impression is conveyed by comparing figures 3 *A* and *D*, 4 *B* and 5 *A*. The colored illustrations of this cell in Émile-Weil and Perlès' monograph [16] on sternal puncture compared with the

16. Émile-Weil, P., and Perlès, S.: La ponction sternale, Paris, Masson & Cie, 1938, p. 29.

cell in figure 2 *C* seem to support this supposition. Not infrequently the nucleus succeeds in completely dividing, with the formation of multinuclear giant cells.

Much about the origin of platelets has already been said in this report. Figure 5 presents the facts more clearly than words can do. The formation of platelets seems to commence in the promegakaryocytic phase, and they may be detached and thrown into the peripheral circulation at any moment. What I designated as a third variety of platelets found in the smear of the peripheral blood is a misnomer, since in reality this "third variety" consists of torn parts of the cytoplasm of the type of megakaryocyte destined for phagocytosis.

SUMMARY

A case of a reaction of the bone marrow not previously described in medical literature is reported. This reaction consists of myeloid, erythroid and megakaryocytic hyperplasia, with preponderance of the last. It is clinically manifested by a microcytic hypochromic anemia, unrelieved by massive doses of iron. The cause is unknown.

The numerous megakaryocytes present afford an opportunity to study their character, origin and development.

A criterion for the determination of the age of a given cell, based on the cytoplasm rather than on the nucleus, is explained and justified. The behavior of the nucleus and of the cytoplasm is delineated separately with a view to explain the dissociation in their development and to establishing a suitable standpoint for the proper observation and interpretation of the different normal and abnormal variations.

The different fates of the megakaryocytic cytoplasm are discussed, one of which is the formation of platelets.

Dr. Eugen Stransky first called my attention to the uniqueness of the case and urged me to write a report of it. Dr. A. Legarda and Dr. E. Medina-Cué supplied the photomicrographs. Permission to report this case was given by the late Dr. G. Ocampo, whose staff cooperated in the preparation of this report.

OBJECTIVE AND CLINICAL STUDY OF THE TONGUE

Comparison of Normal, Desquamated and Atrophic Tongues by a Tongue Print Method

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BROOKLYN

THE REALIZATION that changes in the tongue are a consistent and reliable indication of certain deficiency states has led to many sporadic attempts to place observation of the tongue on a measurable basis. Oatway and Middleton [1] used smoked paper to make tongue prints; Kruse [2] utilized microscopy, and others have tried both monochromatic and color photography. Unfortunately, none of these methods have the virtue of being both simple and accurate. Moreover, none of them actually yield data which can be recorded and measured. Smoked paper prints are meritorious, except that they are negative images and the smoked paper is difficult to prepare and to transport. An added disadvantage is the need for shellacking to make permanent records. Biomicroscopy is difficult for both observer and patient. While color photography produces dramatic and striking pictures, it still does not provide an accurate record and is subject to the same optical inaccuracies encountered in monochromatic photography, namely, failure to record faithfully changes in surface contour.

This contribution is made in an effort to devise a simple, cheap and accurate method of recording surface changes in the tongue. It is further intended to describe the variations encountered in the normal tongue and, finally, to demonstrate the uses of this method in certain clinical entities.

METHODS

An inking solution is made by heating at boiling temperature for ten minutes in a water bath 2 Gm. of Evan's blue and 10 Gm. of gum acacia in 40 cc. of distilled water. When the solution is cool, a few drops of chlorobutanol may be added to prevent the growth of molds. This solution will be the consistency of thick cream, odorless, tasteless and nonpoisonous. It has excellent spreading and printing qualities. Moreover, it dries rapidly and is permanent.

Printing paper should be heavy bond and should be well glazed at least on one surface. Kymograph paper serves the purpose admirably. It is cut up in

From the Department of Medicine of the Long Island College of Medicine and the Kings County and Long Island College Hospitals.

1. Oatway, W. H., Jr., and Middleton, W. S.: Correlation of Lingual Changes with Clinical Data, Arch. Int. Med. **49**:860 (May) 1932.

2. Kruse, H. D.: The Lingual Manifestations of Aniacinosis, with Special Consideration of the Detection of Early Changes by Biomicroscopy, Milbank Mem. Fund Quart. **20**:262, 1942.

oblong strips 12 by 16 cm. and clipped to a backing of stiff cardboard. A supply of this paper, the inking solution and a number of sterile 4 by 4 in. (10 by 10 cm.) gauze pads are all the materials needed to make observations.

In practice, the patient is asked to protrude his tongue in a relaxed state with his mouth slightly open. He is warned not to retract it until told to do so. Some difficulty is encountered in patients who contract their tongue when protruding it, but a demonstration by the observer will in most cases solve this problem. Prints of the tongue protruded in a contracted state are not accurate, and this error must be carefully avoided. Also, it is desirable to protrude the tongue only about 1 inch (2.5 cm.) from the margin of the teeth, as most persons cannot protrude it farther than this in the relaxed state. The tongue is then dried thoroughly with the sterile gauze. A generous amount of the inking solution is applied with another piece of sterile gauze. The solution should be well worked over the distal third of the tongue, including the tip and as much of the mar-

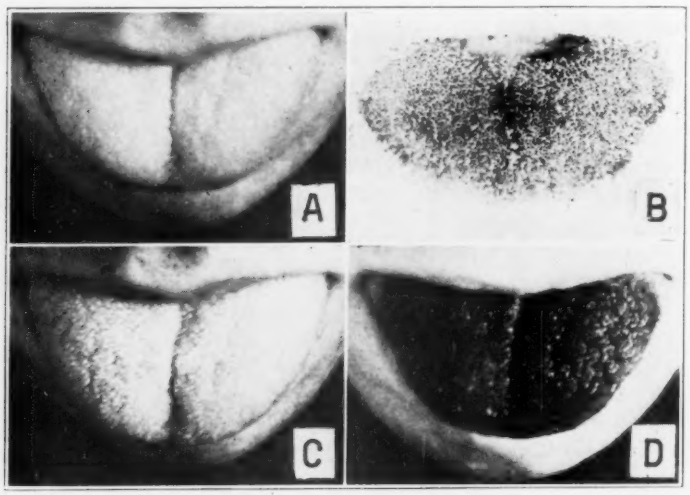

Fig. 1.—Photographs, taken under different conditions, of a normal tongue of the filiform, slightly fissured type compared with its print. In *A* the tongue has saliva on it, while in *C* it has been dried. When the inking solution is applied, the appearance is as in *D*. Note in the print, *B*, that the mucous membrane of the tongue is thrown up into folds; every detail is recorded faithfully, including the papillae and the folds and creases.

gins as possible. The excess ink is then blotted off with a third piece of gauze. By gently but evenly pressing the backed paper against the tongue, three or four successive prints may be made. This must be done rapidly, for the ink dries on the tongue in a few seconds. One of the prints made will generally be satisfactory, showing great detail. If none is acceptable the whole process must be repeated from the start because satisfactory printing depends on having just the right amount of ink of the proper consistency on the tongue. This knack is the secret of the whole process, but, fortunately, it is easily learned with practice.

With some patients, difficulty will be encountered from excessive salivation. This leads to dilution of the ink and blurring of the print. It is easily avoided

by placing dentist's rolls in the patient's mouth on each side over the opening of the salivary ducts beneath the tongue.

RESULTS

Interpretation of Tongue Prints.—An average normal tongue print is shown in figure 1 *B*. The detail is great and withstands scrutiny with a hand lens. The photograph of the same tongue (fig. 1 *A*) with saliva on it shows little detail; in fact, one might suspect it to be a so-called smooth tongue. A better picture is obtained when the tongue is dried, (fig. 1 *C*) but this still does not permit accurate study. When the inking solution is applied as in figure 1 *D*, a further detail is noted in the photograph: namely, the mucous membrane of the normal tongue is often thrown up in folds and resembles a mulberry. This produces small fissures on the surface. Not all tongues have this feature, as will be shown subsequently, but it is notable that such small fissures are recorded faithfully in the print, whereas they are

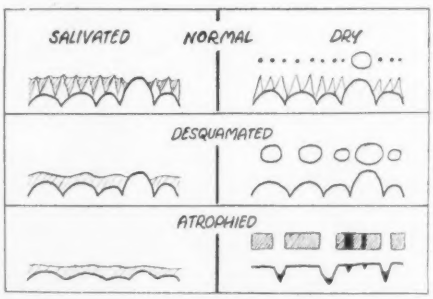

Fig. 2.—Schematic representation of the surface of the tongue showing why it appears smoother when salivated. A projection of the cross sections shows how the papillae and fissures will print.

difficult to discern in the photograph. The obvious conclusion to be drawn is that simple direct printing of the tongue by the method described is more useful than photographing it.

In order to understand the detail in the prints, it is necessary to be cognizant of both the surface anatomy of the tongue and the mechanics of the printing which registers these structures. Fortunately, only three features of the surface of the tongue enter into the problem. These are the filiform papillae, the fungiform papillae and the underlying folds, fissures or creases in the mucous membrane. With this method only the distal third of the tongue can be conveniently studied; hence the structures present on the proximal two thirds of the tongue are not included. With a little imagination, and by reference to figure 2, it will be easily perceived how these structures will print. The filiform papillae, which are small cornified tufts of epithelium

with two or three points to them, will pick up a minute drop of ink and print as either a round or, more frequently, a star-shaped dot. On the other hand, the fungiform papillae, which are larger and smooth, pick up little ink. Because the ink dries rapidly, the domed surface will not print at all, and only the sloped sides, which retain a little ink in the crevices, will print. As a result, fungiform papillae come out in the print as round "cheese holes." Figure 3 *C* shows typical filiform papillae magnified twelve times, while figure 3 *D* shows a

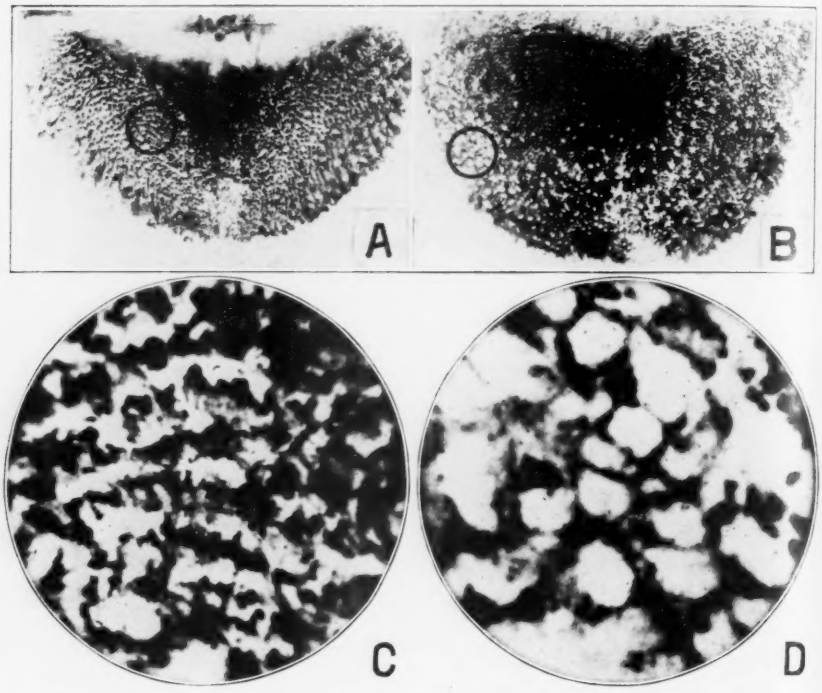

Fig. 3.—Two types of normal tongues: *A*, linear and *B*, fungiform. Enlargements (× 12) of the surface structure; *C*, detail of filiform papillae and their linear arrangement; *D*, detail of a group of fungiform papillae.

group of fungiform papillae at the same magnification. When the tongue atrophies, the surface flattens and papillary structure disappears; it may be expected to print as a monotone, interrupted only by dark lines of smaller fissures and larger linear blanks of the deeper fissures, which are not filled with ink and thus do not print (figs. 2 and 4).

Enumeration of the Papillae.—By study of a group of 99 healthy men who were medical students in the third decade of life and who

were theoretically on adequate diets, certain features and variations of the normal tongue could be defined. First of all, an attempt was made to enumerate the number of fungiform and filiform papillae seen on the prints. It would be too tedious, if not impossible, to count all the papillae obtained in each print. Instead, the counting was restricted to circles exactly 0.5 cm. in diameter which were drawn with india ink on the tongue prints. The center of the circle for enumeration of the filiform papillae was always placed at a point 1 cm. from the

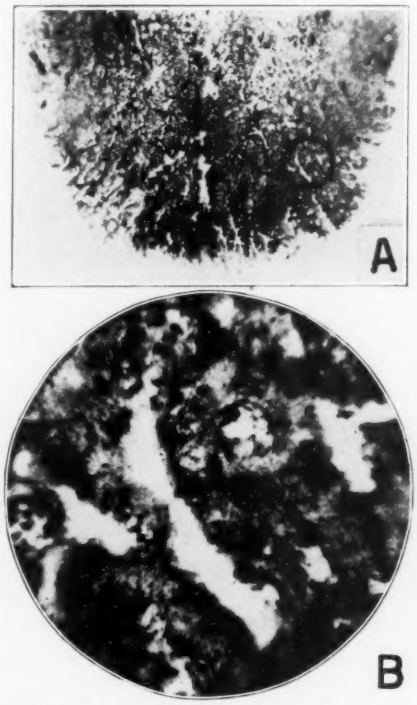

Fig. 4.—*A*, the print and *B*, the enlargement (× 12) of the atrophic tongue of patient J. J. (see table 3). Note the sharp creases and grooves of the surface, with complete absence of papillary structure.

midline and 1 cm. from the tip of the tongue, as measured on the tongue print. This was usually a particularly advantageous area, since the filiform papillae were not too crowded, as they were nearer the center of the tongue, yet they were not sparse as they were on the tip and margins. The centers of the circles for the enumeration of the fungiform papillae were always placed on the margins of the tongue.

Usually, three areas were selected which demonstrated the fungiform papillae well, and the results were averaged for a particular tongue.

The results of a papillae count made by this method are summarized in table 1. The average count of filiform papillae on the tongue prints of the entire group was 52.2, and the average count of fungiform papillae was 8.1. The data further show that there is a wide spread from the mean for both types of papillae, while the standard deviation is the high for both. This indicates that there is only a limited usefulness to enumeration of the papillae, since there does not seem to be, judging from the data obtained, a critical level for the number of papillae of the normal tongue. However, this does not obviate its practicability when prints of the same tongue are observed over a period of time or when abnormal tongues are studied, as will be shown subsequently. It must also be pointed out that the counts, particularly for the filiform papillae, may not correspond to a direct anatomic count of the same area. That is, a filiform papilla may print as two distinct dots if it has a bicornate head, whereas it is in reality only one papilla.

TABLE 1.—*Papillae Counts of Normal Tongues*

Papillae	Average	Highest Number	Lowest Number	Standard Deviation
Filiform	52.20	81	34	10.74
Fungiform	8.10	23	3	3.89

Average of counts of papillae on tongue prints of 99 men in the third decade of life (average age 21). Counts are for a circle 0.5 cm. diameter; area 0.196 cc. Center of circle for the filiform papillae count is 1 cm. from tip and 1 cm. from the middle of the tongue. Counts of the fungiform papillae are average counts from 3 similar circles on the margins of tongue.

Types of Tongues.—Comparison of the tongue prints shows that no two tongues are alike. However, there are certain characteristic features which permit grouping the tongues in types. Thus, the tongue in figure 1 *B* shows predominance of the filiform papillae and, as a secondary feature, is slightly fissured. Figure 3 *A* portrays a tongue whose only dominant feature is a linear arrangement of the filiform papillae, while in figure 3 *B* the prominent feature of the tongue is a large number of hypertrophied fungiform papillae scattered over the surface. The normal fissured tongue is shown in figure 5 *D*. A small group of the tongues have slight fissuring as their only dominant feature (not illustrated). The types of tongues observed in 99 medical students are classified in table 2. Approximately two thirds of the group had tongues which showed only one dominant feature, and of these the commonest by far was the filiform type. With the exception of the fungiform type, the others were relatively uncommon. The other third of the group had tongues with a dominant and also a secondary feature. Again in table 2, it may be seen that the filiform, slightly fissured

type was the commonest while the fungiform linear type was next in order of frequency.

The value of such a classification is that it makes available a measuring stick for testing the normalcy of a particular tongue by mere inspec-

TABLE 2.—*Types of Normal Tongues*

Tongues With One Dominant Feature	Number	Tongues With a Dominant Feature Plus a Secondary Feature	Number	Total
Filiform	38	Filiform, slightly fissured	12	50
Fungiform	15	Fungiform, linear	9	24
Fissured slightly	6	Slightly fissured, filiform	5	11
Fissured	5	Fissured, fungiform	4	9
Linear	3	Linear, fungiform	2	5
Total	67		32	99

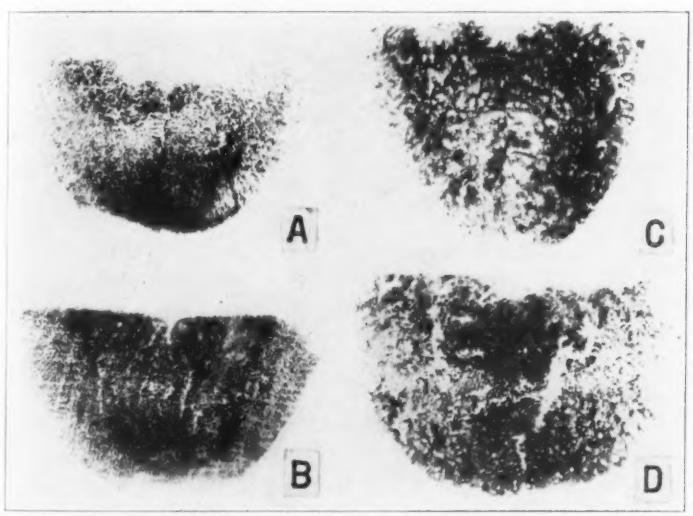

Fig. 5.—Prints illustrating various types of folds and creases of normal and of abnormal tongues. *A* and *B*, tongues of patients with cardiac disease and nephritis, respectively. Both tongues were edematous. Note the horizontal serrations, especially at the margins; the filiform papillae do not print clearly because they are swollen as a result of the edema. *C*, print of the atrophic fissured tongue of a 90 year old avitaminotic patient; *D*, print of the normal, fissured tongue of a medical student. Note that in *D* papillary structure is normal, while in *C* it is completely absent.

tion of the tongue print. In order for a tongue to be classed as normal, it must fit into one of the types specified. Since 50 per cent of normal tongues are of the filiform type, the chances are good that if a tongue in question is of the filiform type it is normal. On the other hand, if a particular tongue is fissured slightly, or even decidedly, it does not

of necessity mean that it is abnormal, since 20 per cent of the tongues which are normal are fissured. The same reasoning applies to prominance of the fungiform papillae, but in this case, as is shown later, only when the filiform papillae are intact.

Features of the Abnormal Tongue.—By study of the prints of the tongues of over 100 patients with definite histories of dietary deficiencies of long standing, the features of the abnormal tongue were elucidated.

TABLE 3.—*Abnormal Features of Tongue Observed in Fifteen Patients with Definite Histories of Dietary Deficiencies*

Name	Age	Sex	Clinical Diagnosis	Filiform Papillae Count	Fungiform Papillae Count	Abnormal Feature of Tongue Shown on Prints	Clinical Appearance of Tongue
J. J.	65	M	Pellagra	7	13	Longitudinal ridging	Smooth, magenta
F. M.	49	M	Chronic alcoholism, avitaminosis	28	6	Longitudinal ridging, cross-hatching	Normal
T. C.	59	M	Diacetylmorphine addict, avitaminosis	23	19	Crosshatching	Normal
A. W.	91	F	Senility, avitaminosis	0	9	Absence of filiform and fungiform papillae	Fissured, raw, red
M. L.	80	F	Arteriosclerosis, avitaminosis	0	7	Crosshatching	Smooth, atrophic
S. L.	65	F	Plummer-Vinson syndrome	3	14	Crosshatching	Smooth, atrophic
H. A.	59	M	Chronic alcoholism, avitaminosis	0	8	Crosshatching	Smooth, magenta
L. B.	71	F	Achlorhydric anemia, avitaminosis	0	17	Crosshatching	Smooth
E. A.	39	M	Chronic alcoholism, cirrhosis of liver	8	7	Crosshatching	Questionably smooth
E. L.	50	M	Peptic ulcer, avitaminosis	18	21	Crosshatching	Smooth
A. K.	44	M	Chronic alcoholism, avitaminosis	3	12	Longitudinal ridging	Smooth, red
A. M.	28	M	Lobar pneumonia, avitaminosis	0	10	Crosshatching	Smooth, red
W. J.	65	M	Beriberi heart (?), avitaminosis	20	19	Crosshatching	Normal
W. C.	40	M	Chronic alcoholism, cirrhosis of liver	0	18	Crosshatching	Smooth
L. S.	64	M	Chronic alcoholism, avitaminosis	5	11	Crosshatching, longitudinal ridging	Smooth, red
			Average	7.7	12.7		

In table 3 are summarized the detailed observations on 15 of these patients selected at random. The striking feature is a pronounced decrease in the number of filiform papillae and a slight increase in the number of fungiform papillae. Thus, the average count of filiform papillae for this group was 7.7, compared with an average count of 52.2 for the normal (table 1); for the fungiform papillae, the average count was 12.7 compared to 8.1 for the normal. Expressed differently, there is in the abnormal tongue a reversal of the normal ratio of filiform to fungiform papillae.

The tongue prints of a group of 7 patients with proved pernicious anemia showed essentially the same changes in the papillae counts. It is noteworthy that after treatment in this group, the papillae counts reverted toward the normal levels (see table 4). Two other features were discovered to be consistently present in the abnormal tongues. One was the appearance of a crosshatched pattern in the print. This is as a rule better seen in heavy prints than in lighter ones (fig. 6). After therapy, this sign has a tendency to disappear. We interpret this to signify a thinning of the mucous membrane of the tongue, so that the impression of the underlying lattice work of fibromuscular structure prints through. Ordinarily the mucous membrane is too thick, particularly when the filiform papillae are intact, for these inner

TABLE 4.—*Abnormal Features of Tongue Observed in Seven Patients with Proved Pernicious Anemia*

Name	Age	Sex	Papillae Count Before Treatment		Papillae Count After Treatment		Abnormal Feature of Tongue Shown on Prints	Clinical Appearance of Tongue
			Filiform	Fungiform	Filiform	Fungiform		
D. V.	61	F	12	2	20	10	Decided longitudinal ridging	Normal
A. B.	59	F	0	14	26	16	Decided longitudinal ridging	Smooth
E. G.	70	F	6	5	11	10	Longitudinal ridging, crosshatching	Smooth
H. B.	57	F	9	15	22	10	Decided longitudinal ridging	Normal
F. K.	54	M	24	9	32	11	Crosshatching	Smooth at edges
S. S.	42	M	0	33	32	11	Crosshatching	Smooth, bald, red
M. W.	79	F	0	10	12	8	Crosshatching	Smooth, red
Average.....			7.3	12.5	22.5	10.4		

structures to print. This crosshatch feature of the print presumably is similar to the horizontal serrations seen grossly on the margins of the tongues of persons suffering from dietary deficiencies. At any rate the crosshatched pattern can be taken as a reliable indication that thinning of the mucous membrane of the tongue has taken place. It has been seen in prints of normal tongues only under conditions leading to increases in hydration, such as exist in patients with cardiac and nephrotic edema (fig. 5 *A* and *B*). As can be seen in tables 3 and 4, it is present in nearly all the prints of the tongues of persons with dietary deficiencies and in 4 prints of the tongues of patients with pernicious anemia.

The other significant feature of abnormal tongues is longitudinal ridging (fig. 7 *A*). In this condition the mucous membrane is thrown up into folds resembling ridges along the longitudinal axis of the tongue. The reason for this may be a diminution in the inner muscular volume of the tongue, which throws the mucous membrane into folds, just as

the skin of an apple wrinkles when it dries. It occurs along the longitudinal axis because the tongue is weaker structurally in its horizontal axis. As additional evidence, it may be pointed out that the tongue of the patient who is dehydrated frequently shows the same feature even on gross inspection. However, in some cases an element of hyperplasia of the mucous membrane may play a part. Others have called this abnormal feature a "scrotal pattern" of the tongue, but we believe the term "longitudinal ridging" to be more accurate and descriptive, though perhaps less colorful.

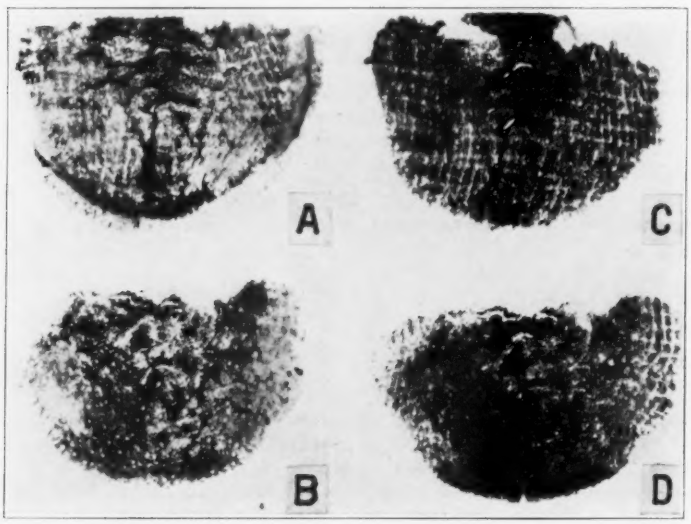

Fig. 6.—Prints of tongue before and after treatment of patient A. M. (table 3), with lobar pneumonia and acute avitaminosis. *A*, the tongue before treatment; complete absence of filiform papillae while groups of normal fungiform papillae remain, producing a desquamated appearance. *B*, appearance decidedly changed after a week's treatment for the patient's disease with nicotinic acid and riboflavin; considerable growth of filiform papillae, while the fungiform papillae have hypertrophied. *C* and *D*, heavier prints taken at the same time as *A* and *B*, respectively. This was done to bring out the crosshatched pattern, which is a distinctive sign of thinning of the mucous membrane.

In tables 3 and 4 it may be seen that longitudinal ridging is much less common than crosshatching. This is because longitudinal ridging is an evanescent sign, and may be present only for a few hours to one or two days. Thus in the case of D. V. (fig. 7 and table 4) the ridging disappeared in three days, after only two injections of extract of liver. Noteworthy is the fact that when ridging is pronounced, crosshatching does not appear in the print.

It may also be shown by study of tables 3 and 4 that there is no distinct separation in type between the tongue of a patient suffering from dietary deficiences and that of one with pernicious anemia. It appears probable that the same element is deficient in each of the 2 patients. In this we concur with Sevringhaus and Kyhos.[3] Incidentally, all our patients with pernicious anemia received adequate daily doses of riboflavin and nicotinamide as part of their treatment.

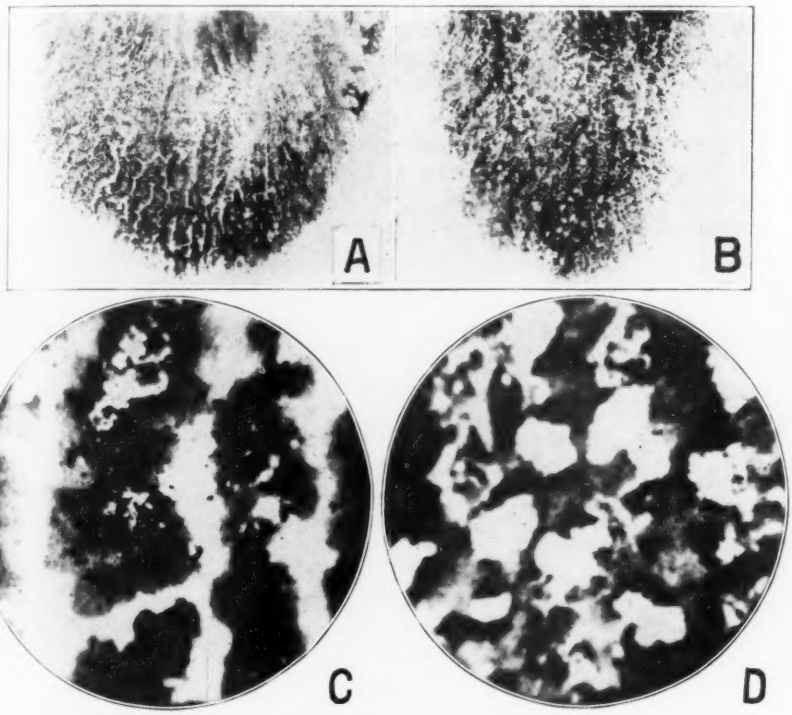

Fig. 7.—Prints (*A* and *B*) and enlargements (*C* and *D*) of the tongue before and after a patient with pernicious anemia was given treatment with extract of liver and with nicotinic acid and riboflavin (see D. V., table 4). *A* and *C*, before treatment; note the longitudinal ridging. *B*, three days later; the ridging has disappeared. The enlargement, *D*, now shows rudimentary hypertrophied fungiform papillary structure.

COMMENT

The plethora of terms descriptive of types of tongues in the medical literature is confusing. Many writers have described a certain type as distinctive of a particular clinical entity. However, it is easier to

3. Sevringhaus, E. L., and Kyhos, E. D.: Reversal of Lingual Atrophic Changes with Nicotinamide Therapy, Arch. Int. Med. **76**:31 (July) 1945.

read the description than it is to pick out such tongues in the ward. What is needed is a classification of the abnormal tongues based on the fundamental mechanism of the pathologic changes. Since the crucial structures on the lingual surface are the papillae, any attempt to define changes in the tongue should be based on them. In figure 8, a chart which aims to clarify the lingual changes encountered in disease, the normal tongue is defined as one with its filiform and fungiform papillae intact both as to number and as to structure. In disease the first tendency is for the tongue to desquamate; that is, the cornified filiform papillae dissolve or wear off from the surface of the tongue. In this stage the tongue is frequently coated. Once desquamated, the tongue lacks protection and is apt to become inflamed, red or swollen. If recovery takes place, the papillae revert to normal; if not, the tongue goes on to atrophy, which is defined as the absence of all filiform papillae and a decided diminution of fungiform papillary structure. Once in this stage the tongue of a patient shows little tendency toward

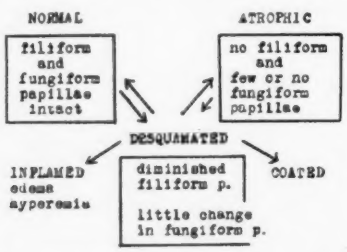

Fig. 8.—Mechanism of the changes causing the abnormal tongue.

recovery even with treatment. In figure 9 *B* is shown the atrophic tongue of an avitaminotic patient 80 years old, with complete absence of papillae. Treatment for three months with large doses of nicotinamide and riboflavin failed to bring about any changes in the tongue (fig. 9 *D*). The tongue of a patient with Plummer-Vinson syndrome (hypochromic anemia) on the other hand, showed some remains of fungiform papillary structure before treatment (fig. 9 *A*). After one month of therapy with iron, thiamine, riboflavin and nicotinamide there was considerable growth of filiform papillae (fig. 9 *C*).

This classification recognizes the fact, often forgotten, that the fungiform papillary structure is the underlying unit of the tongue. It is from the sides of the fungiform papillae that the filiform papillae grow.[4] Hence, even if the filiform papillae disappear, the fungiform papillae should remain. This is exactly what enumeration of the papillae of

4. Smith, P. E.; Copenhaver, W. M.; Severinghaus, A. E., and Goss, C. M.: Bailey's Text-Book of Histology, ed. 11, Baltimore, William Wood & Company, 1944.

normal and abnormal tongues by the print method has demonstrated. Finally, if the tongue is atrophic both types of papillae should disappear, and again proof of that fact can be obtained in serial prints of the tongue which does not respond to therapy.

Therefore, a plea is made to workers in this field to restrict themselves to terms here outlined. Only then can it be discovered whether several factors lead to the development of an abnormal tongue or whether one factor alone is involved. Moreover, the degree of dietary deficiency required to bring about first desquamation and then atrophy of the tongue can be clearly defined, and the response to therapy accurately gaged.

Fig. 9.—Prints selected to demonstrate the difference between the desquamated and the atrophic tongues. *A*, the tongue of patient S. L. (table 3); some fungiform papillary structure remains. Compare with *B*, the tongue of patient M. L. (table 3). *C*, same tongue as *A* after the patient had one month's treatment with iron sulfate, nicotinic acid and riboflavin. There is considerable growth of filiform papillae and hypertrophy of the fungiform papillae. *D*, same tongue as *B* after the patient had three months' treatment with large doses of nicotinic acid and riboflavin. There is no change in surface structure; hence the tongue of *A* must have been desquamated, the tongue of *B* atrophied.

SUMMARY AND CONCLUSIONS

A method has been described which permits accurate printing of the distal third of the tongue. This has been made possible by development of an ink which is nonpoisonous, tasteless, of the proper con-

sistency and fast drying. Prints obtained withstand scrutiny with low powers of the miscroscope and render clear and permanent the detail of the filiform and fungiform papillary structure of the tongue. The underlying folds and creases in the mucous membrane of the tongue are also defined in the prints.

The tongue prints of a group of 99 normal, healthy male medical students were studied by this method. Counts of the filiform and fungiform papillae were made and averaged 52.2 for the former and 8.1 for the latter. It was found that these tongues could be grouped into five distinct types. In the order of frequent occurrence, these types were filiform, fungiform, slightly fissured, fissured and linear.

Prints of the tongues of a group of 15 patients with definite dietary deficiencies and those of a group of 7 patients with pernicious anemia were compared with those of the normal group. It was found that there was a pronounced decrease in the count of filiform papillae and a slight increase in the number of fungiform papillae. Two other distinctly abnormal features, a crosshatched pattern and longitudinal ridging, never found in the normal group, are described and their significance discussed. The tongues of the group of patients with dietary deficiences could not be distinguished from those of the group of patients with pernicious anemia.

A plea is made for a classification of the abnormal tongue based on the fundamental structure of the lingual surface, i. e., the papillae. This classification recognizes only three groups: the normal tongues, which have intact papillae as to both number and structure; the desquamated tongues, which have a pronounced decrease in filiform papillae but have their fungiform papillae intact, and the atrophic tongues, in which there is complete absence of filiform papillae and a decided decrease in fungiform papillae.

RETINAL AND CHOROIDAL ARTERIOLES IN MALIGNANT HYPERTENSION

A Clinical and Pathologic Study of Fifteen Cases *

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SINCE Richard Bright,[1] in 1836, described the renal syndrome which came to bear his name, innumerable authors have contributed to the clarification and classification of renal disease and hypertension. Johnson,[2] in 1868, was the first to describe the presence, in cases of Bright's disease, of a diffuse disease of the smallest arteries characterized by hypertrophy of the media.

At the Mayo clinic, since the papers of Keith [3] and Keith, Wagener and Kernohan,[4] a number of studies [5] have served to emphasize the diffuse nature of hypertensive vascular disease. Beginning with the work of Kernohan, Anderson and Keith,[6] an attempt has been made to establish the normal thickness of the wall of an arteriole as compared

* Abridgment of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Medicine.

1. Bright: Cases and Observations, Illustrative of Renal Disease Accompanied with the Secretion of Albuminous Urine, Guy's Hosp. Rep. **1**:338-400, 1836.

2. Johnson, G.: On Certain Points in the Anatomy and Pathology of Bright's Disease of the Kidney: II. On the Influence of the Minute Blood-Vessels upon the Circulation, Med.-Chir. Tr. London **51**:57-78, 1868.

3. Keith, N. M.: Classification of Hypertension and Clinical Differentiation of the Malignant Type, Am. Heart J. **2**:597-608 (Aug.) 1927.

4. Keith, N. M.; Wagener, H. P., and Kernohan, J. W.: The Syndrome of Malignant Hypertension, Arch. Int. Med. **41**:141-188 (Feb.) 1928.

5. (*a*) Cain, E. F.: Malignant Hypertension: The Histologic Changes in the Kidneys, Arch. Int. Med. **53**:832-850 (June) 1934. (*b*) Kyser, F. A.: Relationship of Essential Hypertension to Pathologic Changes in the Thyroid Gland, Thesis, Graduate School of the University of Minnesota, 1940. (*c*) Morlock, C. G.: Arterioles of the Pancreas, Liver, Gastro-Intestinal Tract and Spleen in Hypertension, Arch. Int. Med. **63**:100-118 (Jan.) 1939. (*d*) Odel, H. M.: Structural Changes in Arterioles of Myocardium in Diffuse Arteriolar Disease with Hypertension Group 4, ibid. **66**:579-602 (Sept.) 1940. (*e*) Rosenberg, E. F.: The Brain in Malignant Hypertension: A Clinicopathologic Study, ibid. **65**:545-586 (March) 1940.

6. Kernohan, J. W.; Anderson, E. W., and Keith, N. M.: The Arterioles in Cases of Hypertension, Arch. Int. Med. **44**:395-423 (Sept.) 1929.

with its lumen and to determine what changes are to be found in hypertension. With a few notable exceptions, to be discussed later, it has been found that although the wall-lumen ratio varies radically in different organs hypertension is uniformly accompanied with a definite reduction of the ratio of the diameter of the lumen to the thickness of the wall. The degree to which it is reduced increases as the severity of the hypertension increases. Furthermore, this reduction has appeared in many instances to be of sufficient degree to present a definite impediment to the flow of blood.

Although, as noted, numerous papers have been concerned with the pathologic anatomy of hypertensive disease, only a few detailed studies of the eyes have been reported.

TABLE 1.—*Summary of Clinical and Pathologic Data on Controls*

Age, Yr.	Sex	Pathologic Diagnosis	Highest Recorded Blood Pressure, Mm. Hg		Body Weight, Lb.	Heart Weight, Gm.	Normal Heart Weight, Gm.*	
			Systolic	Diastolic			Maximum	Minimum
41	M	Lymphoblastoma	130	90	185	350	382	296
57	F	Hyperthyroidism	Preop. 132 Crisis 165	80 112	135	275	286	203
23	F	Torula meningitis	140	80	180	320	356	301
50	F	Ruptured cerebral aneurysm	134	106	150	310	313	225
20	F	Polyneuritis	150	90	121	260	259	215
55	F	Carcinoma of breast	130	80	140	280	295	253
43	F	Carcinoma of common bile duct	100	50	165	237	337	247

* Normal heart weight means the weight of the heart of a normal person of the same age, sex and body weight as the subject (See Smith, H. L.: Relation of Weight of Heart to Weight of Body and of Weight of Heart to Age, Am. Heart J. **4**: 79-93 [Oct.] 1928).

The present study is concerned with eyes which were obtained at necropsy in 15 cases of malignant hypertension. The work was directed mainly toward lesions of the arterioles and more particularly to a determination of the change which might be found in the wall-lumen ratio of arterioles of the retina and the choroid. Seven additional cases were selected as controls, in which neither the history nor the physical examination showed any evidence of hypertension (table 1).

REVIEW OF LITERATURE

Bright,[1] in his paper of 1836, remarked that patients who have nephritis often suffer from visual impairment.

Türck,[7] in 1850, first reported microscopic lesions in the eyes of nephritic patients when he found "an exudative process" with the presence of "granular cells in the posterior portion of the retina."

7. Cited by Greear.[20]

Liebreich [7] described "albuminuric retinitis," and Weeks [8] found that in such cases there was irregular hyaline degeneration of the retinal and choroidal arteries with encroachment on the lumen.

In cases of angiosclerosis, Coats [9] found eccentric proliferation of the endothelium with narrowing of the lumen.

Leber [10] stated that in cases of retinitis due to nephritis the central retinal and posterior ciliary arteries showed medial hypertrophy.

Cohen,[11] in reporting the histologic changes in the eyes in 18 cases of "general arterial and kidney diseases," included 3 cases of malignant hypertension. In these he found severe sclerosis of the choroidal arterioles, compared with moderate sclerosis of the retinal arterioles. The vascular changes were not proportionate to those seen ophthalmoscopically.

Wagener,[12] in 1927, described the retinopathy of malignant hypertension and included histologic studies of 3 cases. The retinal arterioles were thickened principally by perivascular fibrosis. There was slight medial hypertrophy but no intimal hyperplasia. The internal elastic lamina was slightly thickened. Choroidal arteriosclerosis was more severe than retinal, and there were also medial hypertrophy and endothelial hyperplasia. In some cases the lumen was occluded by retinal proliferation, while in others it was filled with fatty granular cells.

Verwey [13] gave a detailed report of the histologic changes in 1 case of albuminuric retinitis. His observations were essentially the same as Wagener's. Fat staining showed the arteriolar walls thickened by deposits of lipoid material.

Keith, Wagener and Kernohan,[4] in a study of malignant hypertension, found the choroidal to exceed the retinal arteriosclerosis. The retinal arterioles were thickened mainly by medial hypertrophy and perivascular fibrosis, while in the choroidal arterioles the main change was

8. Weeks, J. E.: A Contribution to the Pathology of Albuminuric Retinitis, Arch. Ophth. **17**:276-294, 1888.

9. Coats, G.: Intraocular Vascular Disease, Ophthalmoscope **4**:605-621 (Nov.) 1906.

10. Leber, T.: Die Krankheiten der Netzhaut, in Graefe, A., and Saemisch, T.: Handbuch der gesamten Augenheilkunde, Leipzig, Wilhelm Engelmann, 1915, vol. 7A, pt. 1, pp. 101-106.

11. Cohen, M.: Significance of Pathologic Changes in Fundus in General Arterial and Kidney Diseases, J. A. M. A. **78**:1694-1698 (June 3) 1922; Chorioretinal Arteriolar Necrosis in Malignant Hypertension: Report of a Case, Arch. Ophth. **23**:1052-1059 (May) 1940.

12. Wagener, H. P.: The Retinitis of Malignant Hypertension, Tr. Am. Ophth. Soc. **25**:349-380, 1927.

13. de la Fontaine Verwey, B. C.: Ueber die Arteriosklerose der Netzhaut und ihre Bedeutung für die Genese der Retinitis albuminurica, Klin. Monatsbl. f. Augenh. **79**:148-158 (Sept. 2) 1927.

intimal proliferation, with less striking medial hypertrophy and perivascular fibrosis.

Friedenwald [14] stated that the vascular lesions of albuminuric retinitis are the same as those of malignant hypertension. He emphasized the occurrence of acute necrosis with hyalinization and the diffusion of lipoid material in the arteriolar walls.

In cases of albuminuric retinitis Kyrieleis [15] found arteriosclerotic changes present consistently in the optic disk but not in the retina.

Moritz and Oldt [16] found that in the eye arterioles having an external diameter of 50 to 100 microns showed intimal hyalinization. In those vessels larger than 50 microns there was frequently also endothelial proliferation.

Gasteiger [17] in cases of malignant nephrosclerosis found the retinal arterioles thickened by fat infiltration, accompanied with a decrease of the lumen. Similar but more severe changes were seen in the choroidal arterioles.

Koyanagi,[18] some of whose cases appear to have been cases of malignant hypertension, found that the arterioles of the optic disk and the surrounding retina showed severe endothelial proliferation and hyalinization leading to obliteration of the lumen. There were similar severe changes in the choroidal arterioles.

Magitot and Dubois-Poulsen,[19] in a case of malignant hypertension, found patchy arteriolar lesions which were more severe in the choroid than in the retina. There were intimal proliferation with encroachment on the lumen, fat infiltration of the proliferated cells and medial hypertrophy.

Greear [20] found medial hypertrophy and hyalinization in the retinal arterioles and more severe changes in the choroidal arterioles.

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14. Friedenwald, H.: Pathological Changes in the Retinal Blood-Vessels in Arterio-Sclerosis and Hypertension, Tr. Ophth. Soc. U. Kingdom **50**:452-531, 1930.

15. Kyrieleis, W.: Ueber die Arteriolosklerose von Netzhaut, Aderhaut und Sehnerv sowie ihre Bedeutung für die Pathogenese der Retinitis albuminurica, Arch. f. Augenh. **103**:161-198 (June) 1930.

16. Moritz, A. R., and Oldt, M. R.: Arteriolar Sclerosis in Hypertensive and Nonhypertensive Individuals, Am. J. Path. **13**:679-728 (Sept.) 1937.

17. Gasteiger, H.: Ueber histologische Befunde am Auge bei Nieren- und Blutdruckveränderungen, Klin. Monatsbl. f. Augenh. **99**:604-625 (Nov.) 1937.

18. Koyanagi, Y.: Veränderungen an der Netzhaut bei Hochdruck, pathologische Anatomie, Internat. Ophth. Cong. (1937) **1**:143-283, 1938.

19. Magitot, A., and Dubois-Poulsen: Étude anatomique d'une rétinite apparue au cours d'une hypertension maligne, Ann. d'anat. path. **15**:907-913 (Nov.) 1938.

20. Greear, J. N.: The Eye in Hypertensive Cardiovascular Disease: A Comparative Ophthalmoscopic and Pathologic Study, Tr. Am. Ophth. Soc. **38**: 397-469, 1940.

Agatston [21] found arterioles of the eyes of hypertensive persons to show hyaline degeneration of the intima, swelling of the subendothelial collagen and thickening of the media due to increase of muscle or increase of collagen or both.

CLINICAL STUDIES

Fifteen cases of malignant hypertension were studied. The patients were 1 white woman, 1 Negro man and 13 white men. Their ages varied from 22 to 65 as shown in table 2.

The duration of the disease from the onset of symptoms to death ranged from five weeks to sixty-nine months, with the average duration of sixteen months. One patient (case 13) had been known to have hypertension for two years but had had symptoms only during the last six months of his illness.

The past medical history contributed information in only 4 cases (4, 6, 8 and 9). Besides the usual childhood exanthems, typhoid and

TABLE 2.—*Age Distribution of Patients Who Had Malignant Hypertension*

Age, Yr.	Patients
20-29	2
30-39	3
40-49	1
50-59	7
60-69	2

pneumonia each occurred twice; rheumatic fever and pleurisy with effusion occurred once. In no case was there an antecedent history of glomerulonephritis.

The family history revealed hypertension in one or both parents in cases 3, 6 and 10 and in two siblings in case 11.

The first symptoms to appear were renal in 6 cases (frequency, nocturia or hematuria) and cardiac in 5 cases (dyspnea). Headache, confusion and loss of visual acuity account for the remainder. In table 3 the most significant symptoms are listed in the order of their frequency of occurrence. In 1 case (case 11), in which the onset of symptoms resembled renal colic, the patient had been found at operation to have an aneurysm of the renal artery, and nephrectomy had been done. In another (case 15), in which the first symptom was painless hematuria, ureterolithiasis of the left side and atrophic kidney were observed at necropsy.

A physical examination revealed in each case a noticeable elevation of the blood pressure, with the maximal systolic pressure varying from

21. Agatston, S. A.: Relation of Vascular Disease to Retinitis, M. Rec. **153**: 303-306 (May 7) 1941.

220 to 350 mm. of mercury and the maximal diastolic pressure from 140 to 200 mm.

In every case there was retinopathy of malignant hypertension.

Cardiac enlargement was found in every case and sclerosis of the peripheral arteries (radial, brachial or temporal) in all but 3 cases (5, 8 and 15). Disturbances of cardiac rhythm were recorded in 9 cases: tachycardia in 6, gallop rhythm in 3, extrasystoles in 2 and auricular fibrillation in 1. The aortic second sound was accentuated in 9, and an aortic systolic murmur was heard in 6. A pericardial friction rub was heard in 2 cases (2 and 6). Manifestations of cardiac failure occurred in 10 cases. Pulmonary congestion was present 9 times, enlargement of the liver 5 times, edema and cyanosis each 4 times and ascites once.

Signs referable to the central nervous system were present in 10 instances. Cheyne-Stokes respirations were observed eight times, convulsions twice, hemiplegia twice and muscular twitchings once. Enlargement of the thyroid gland was recorded in 2 cases.

TABLE 3.—*Symptoms in Cases of Malignant Hypertension*

Symptoms	Frequency *
Cardiac Dyspnea, edema, ascites, palpitations	22
Central nervous system Headache, confusion, coma, stupor, convulsions, paralysis	18
General Generalized weakness, loss of weight	15
Visual Blurring, partial to complete blindness	10
Renal Urinary frequency, nocturia, hematuria	9
Gastrointestinal Nausea and vomiting, diarrhea, gastrointestinal bleeding	3

* Frequency means the total frequency of symptoms of this group.

LABORATORY STUDIES

The maximal specific gravity of the urine varied from 1.006 to 1.025 and the minimum from 1.004 to 1.015. In only 3 cases was the specific gravity as great as 1.020. Albuminuria was absent in only 1 case; in 4 it was graded 1 or 2 (on the basis of 1 to 4, in which 1 designates the mildest and 4 the most severe condition) and in the remaining 10 it was 3 to 4. In 4 cases there were no erythrocytes in the urine, while in the remainder the grade varied from 1 to 4. Casts were present in the urine in only 5 cases, and then there were only a few of the granular or the hyaline type.

The concentration of hemoglobin varied from 8.5 to 14.7 Gm. per hundred cubic centimeters of blood in the 14 cases in which it was determined. Leukocytes varied from 5,800 to 19,200 per cubic millimeter of

blood, and there was more than a maximal normal of 10,000 in 7 of the 14 cases in which they were determined. Erythrocytes varied from 2,250,000 to 4,770,000 per cubic millimeter of blood. In 7 cases there was definite anemia as indicated by either a concentration of hemoglobin of less than 12.0 Gm. per hundred cubic centimeters of blood or an erythrocyte count of less than 4,000,000 per cubic millimeter of blood. The concentration of urea was less than 40 mg. per hundred cubic centimeters of blood on admission in only 2 cases (1 and 11), and in each of these it became elevated terminally. The concentration of urea ranged from 33 to 304 mg. per hundred cubic centimeters of blood on admission and from 84 to 492 mg. per hundred cubic centimeters terminally. Terminal concentrations of creatinine varied from 3.0 to 19.2 mg. per hundred cubic centimeters of blood in the 13 cases in which they were determined. Serum sulfates were determined in 6 cases and varied from 5.0 to 49.0 mg. per hundred cubic centimeters of serum. They were definitely more than 5.5 mg. in 5 of the 6 cases in which they were determined.

The concentration of chlorides, determined in 8 cases, was normal in all except 1 (case 14), in which it was subnormal (464 mg. per hundred cubic centimeters of plasma).

The carbon dioxide–combining power was sufficiently depressed to indicate definite acidosis (less than 40 volumes per hundred cubic centimeters of plasma) in only 2 of the 11 cases in which it was determined, but it was less than 50 volumes per hundred cubic centimeters of plasma in an additional 4 cases.

The concentration of potassium was determined in 3 cases and was elevated in 2 (normal 17 to 21 mg. per hundred cubic centimeters of serum).

The serologic reaction of the blood for syphilis was negative in the 12 cases in which it was determined.

Electrocardiograms were taken in 11 cases, and each showed some deviation from the normal. Preponderance of the left ventricle was seen in 6 cases. Changes of the T wave (diphasic or inverted) were found in 8 cases. They were present in lead I alone in 3 cases; they were present in all three standard leads in 4 cases, and in 1 case they were present in leads I, II and IV. Slurring of the QRS complex was present twice in all three standard leads and twice in leads I and III alone. The S-T segment was elevated in CR2 once and depressed once. The clinical and laboratory data are summarized in table 4.

SUMMARY OF GROSS PATHOLOGIC STUDIES

The known duration of the disease from the onset of symptoms to death varied from five weeks to sixty-nine months, with an average duration of sixteen months. The primary cause of death was cardiac failure

TABLE 4.—*Summary of Clinical and Laboratory Data: Malignant Hypertension*

Case	Age, Yr.	Sex	Date of Admission	Blood Pressure, Mm. of Mercury				Urine				Blood										
				Maximum		Minimum		Specific Gravity		Albumin, Grade*	Erythrocytes, Grade*	Casts, Grade*	Hemoglobin, Gm. per 100 Cc.	Erythrocytes, Millions per Cu. Mm.	Leukocytes per Cu. Mm.	Urea, Mg. per 100 Cc.	Creatinine, Mg. per 100 Cc.	Sulfates, Mg. per 100 Cc. of Serum	Chlorides, Mg. per 100 Cc. of Plasma	Potassium, Mg. per 100 Cc. Serum	Plasma CO_2-Combining Power, Vol per 100 Cc.	Flocculation Test for Syphilis
				S.	D.	S.	D.	Maximum	Minimum													
1	55	F	12/ 6/23	260	160	210	130	1.018	1.009	1-3	0	0-1	13.2	4.71	10,400	33 to 134	1.8 to 7.4	....	...	..	..	Neg.
2	50	M	11/13/24	220	140	184	90	1.013	1.013	0	0	0	8.6	2.43	19,200	201 to 255	7.1 to 19.1	....	...	..	..	Neg.
3	65	M	8/11/25	280	150	188	108	1.018	1.012	1	0	0	11.5	3.95	16,800	49 to 101	2.0 to 4.5	....	...	..	45 to 53	.....
4	50	M	1/27/27	260	180	180	90	1.006	1.006	1-2	0-1	0	14.7	3.17 to 4.00	16,800	88 to 158	4.3 to 6.5	....	650	..	55	Neg.
5	22	M	5/ 5/33	350	190	244	162	1.009	1.008	3	3	0	12.3	4.06	8,400	66 to 108	3.8	....	479	..	46.6	Neg.
6	29	M	10/ 4/33	240	150	164	75	1.021	1.010	3	2-4	1-1+† 1-3‡	8.5	2.34	6,400	144 to 492	9.6 to 17.2	15.0 to 17.0	520	..	62.6	Neg.
7	55	M	8/21/34	290	190	194	110	1.014	1.010	3	1	0	10.4	3.71	8,700	154 to 285	6.4 to 8.4	17.7	...	..	39.0	Neg.
8	32	M	2/11/35	240	140	190	86	1.011	1.007	3-4	2-4	0	9.8	3.03	11,200	152 to 324	10.8 to 18.8	....	...	..	..	.....
9	32	M	11/14/38	220	140	190	110	1.012	1.010	3	0-2	0	....	2.25	5,800	304 to 314	16 to 19.2	35.7 to 49.0	544 to 606	23.7	40.0	.....
10	33	M	1/ 2/40	250	162	210	108	1.015	1.008	2-4	1	0	8.5	....	6,600	160 to 284	6.8 to 10.4	....	538	..	59.8	Neg.
11	51	M	2/ 4/42	260	160	180	118	1.025	1.011	2	1	0	12.1	....	6,500	34 to 84	...	....	...	..	..	Neg.
12	63	M	4/21/43	260	170	180	125	1.020	1.015	2-4	0-1	0-1	14.0	....	8,300	42 to 170	1.8 to 3.0	5.0	594	..	58.9	Neg.
13	53	M	9/ 1/43	260	160	230	130	1.012	1.006	2	0	0	12.5	....	.....	213 to 318	8.0	23.2	611	18.7	44.7	Neg.
14	53	M	11/ 1/44	245	200	200	120	1.014	1.004	4-1	1-2	0-2	12.5	4.08	10,300	128 to 324	6.3 to 11.6	14.0	464	33.4	31.0	Neg.
15	43	M	12/10/43	230	150	85	65	1.015	.....	3	4	1	12.3	4.77	11,600	72 to 130	...	....	...	..	41.9	Neg.

* The grade was on a basis of 1 to 4.

† This cast was hyaline.

‡ These casts were granular.

in 4 cases, renal failure in 3, combined cardiorenal failure in 5 and cerebral hemorrhage in 2 cases. In the remaining case, a clinical diagnosis of cerebral hemorrhage was made, but this was not substantiated at necropsy. In addition, in 4 cases there were multiple small (up to 1.0 cm.) or petechial hemorrhages scattered widely through the brain, and in case 13 old infarcts were found in the basal ganglions.

Cardiac hypertrophy was found in every case, as may be seen by referring to the heart weights. In the cases of hypertension the weights ranged from 405 to 870 Gm. compared with a normal range of 275 to 393 Gm. In no case were valvular lesions found which could account for the hypertrophy. Patchy myocardial fibrosis was noted in 5 cases. In case 10 there was an acute infarction of the posterior papillaris muscle of the left ventricle. Coronary arteriosclerosis was found to be mild in 6 cases, moderate in 7 and severe in 2 cases. There was fibrinous pericarditis in 4 cases. Aortic arteriosclerosis was graded as mild in 3 cases, moderate in 8 and severe in 3; in 1 case the grade was not recorded. Pleural effusion was present in 5 instances and pericardial effusion in 2. Pulmonary edema was found 6 times.

The combined weights of the kidneys varied from 144 to 353 Gm. In case 4 a solitary left kidney weighed 166 Gm., while in case 11 the solitary right kidney weighed 185 Gm. In all cases except 2 (5 and 11), there were pitting and scarring of the surfaces of the kidneys. These data are summarized in table 5.

HISTOLOGIC STUDIES

In 3 cases of hypertension the eyes were prepared for sectioning by the celloidin [22] method; in the remaining cases and in the controls the eyes were embedded in paraffin, and the usual fixation by means of solution of formaldehyde was used. Sections were cut so as to include the nerve head and the macular area. The tissues were stained with hematoxylin and eosin, Van Gieson's stain and elastin H stain.

In the control series, all the arterioles of both the retina and the choroid appeared normal (fig. 1). No lesions were seen which could be attributed to aging.

Cases of Malignant Hypertension.—(*a*) Vascular Lesions: 1. Intimal proliferation (subendothelial) occurred frequently and extensively in the arterioles of the choroid (fig. 2 *A*) but only rarely in those of the retina. It was seen in all but 3 of the cases and frequently resulted in partial or even complete obliteration of the lumen. Hyaline degeneration and fatty infiltration of the proliferated intima were seen occasionally.

22. Celloidin is a concentrated preparation of pyroxylin.

* The grade was on a basis of 1 to 4. † This cast was hyaline. ‡ These casts were granular.

TABLE 5.—*Summary of Pathologic Data on Malignant Hypertension*

Case	Duration of Life After Onset of Symptoms	Clinical Impressions as to Cause of Death	Heart Weight, Gm.	Normal Heart Weight, Gm.	Coronary Sclerosis *	Pericarditis	Infarct	Myocardial Fibrosis	Aortic Sclerosis *	Cerebral Hemorrhages	Pleural Effusion	Pericardial Effusion	Ascites	Pulmonary Edema	Combined Kidney Weight, Gm.	Kidneys Pitted and Scarred
1	5 yr. 9 mo.	Cardiac and renal failure	838	393	3	0	0	+	Severe	Multiple small	0	50 cc.	0	Right	300	+
2	3 mo.	Renal failure	623	284	2	+	0	0	1+	0	0	0	0	0	254	+
3	7 mo.	Cardiac failure	496	...	3	0	0	0	2+	Multiple small	0	0	0	0	206	+
4	1 yr.	Cardiac and renal failure	870	300	1	0	0	Slight	2	0	1,000 cc. left	150 cc.	0	0	Left only 166	+
5	7 mo.	Cerebral hemorrhage	722	300	1	0	0	0	1	Massive	0	0	0	+	270	0
6	9 mo.	Renal and cardiac failure	405	275	1	+	0	0	1+	Diffuse petechial	1,000 cc.	0	0	+	144	+
7	5 yr.	Cardiac failure	778	300	1	0	0	0	?	0	0	0	0	0	276	+
8	5 mo.	Renal failure	490	300	1+	0	0	0	1	Multiple petechial	+	0	0	+	...	+
9	2 mo.	Renal failure	595	300	1	0	0	0	1	0	250 cc. right	0	0	+	...	..
10	9 mo.	Cardiac and renal failure	640	300	2	+	+	0	1+	0	0	0	0	0	353	+
11	1½ yr.	Cerebral vascular accident	490	294	2	0	0	0	2	Massive	0	0	0	0	Right, only 185, compensatory hypert.	0
12	2 yr.	Cardiac failure	530	325	2	0	0	1	1+	0	0	0	0	0	243	+
13	6 mo.	Cardiac and renal failure	562	300	1	+	0	+	3	Old infarcts of basal ganglions	+	0	+	+	282	+
14	6 mo.	Cardiac failure	517	360	2	0	0	+	2	0	0	0	0	0	272	+
15	5 wk.	Cerebral hemorrhage not found at necropsy	595	323	2	0	0	0	2	0	0	0	0	0	308	+

* The sclerosis graded as 1 was mild; 1+ or 2, moderate, and 2+ or 3, severe.

2. Medial thickening due to hypertrophy of the muscle cells was seen in every case (fig. 2 *B* and 3 *A*). It was a considerable factor in decreasing the lumen in the retinal but not in the choroidal arterioles.

3. Around both the retinal and the choroidal arterioles an increase of the perivascular fibrous tissue, indistinguishable from the adventitia, was seen in a few instances.

4. Hyaline degeneration (fig. 3 *B*) of varying degree was seen frequently in the choroidal arterioles. This varied from small subendothelial deposits to involvement of the entire wall.

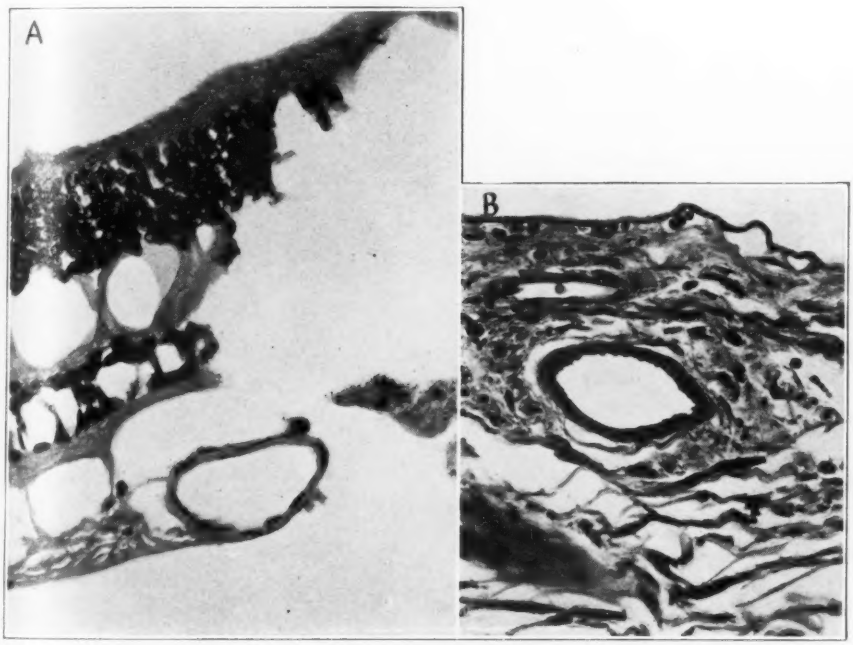

Fig. 1.—*A*, section of normal retinal arteriole (hematoxylin and eosin; × 365). *B*, section of a normal choroidal arteriole (hematoxylin and eosin; × 365).

5. In a few choroidal arterioles there were smudgy granular areas which stained purple with hematoxylin and eosin, indicating acute necrosis. This most often occurred in the thickened intima, but in some instances it also involved the media.

An occasional choroidal arteriole showed infiltration (fig. 3 *C*) of its wall with fat, and some showed reduplication of the elastic lamina (fig. 3 *D*).

(*b*) Retinal Lesions: The histologic lesions, with the exception of those occurring in the arterioles, were found largely confined to an area around the nerve head, comprising about a sixth of the retina. Edema

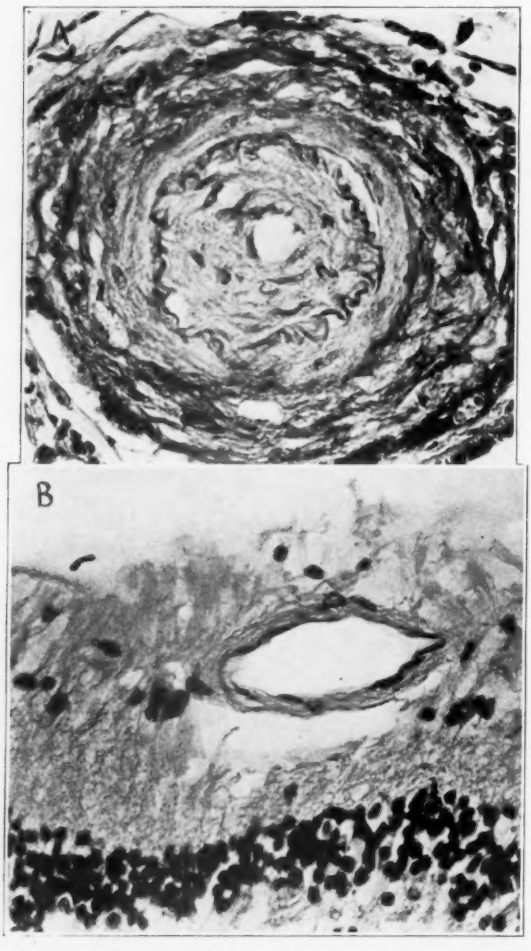

Fig. 2.—*A*, section of a choroidal arteriole of a patient with malignant hypertension (case 10), showing intimal proliferation, medial hypertrophy and perivascular fibrosis (Van Gieson's stain; × 365). *B*, section of a retinal arteriole of the same patient, showing slight medial hypertrophy (hematoxylin and eosin; × 365).

of the nerve head and of the peripapillary portion of the retina was seen in every case. The latter was the most striking of all the lesions seen.

In many cases it was of tremendous degree, producing great distortion of the retina, so that sometimes the retina was thrown into folds, with or without a collection of underlying fluid. In almost all cases there were varying numbers of cytoid bodies in the nerve fiber layers, as well as

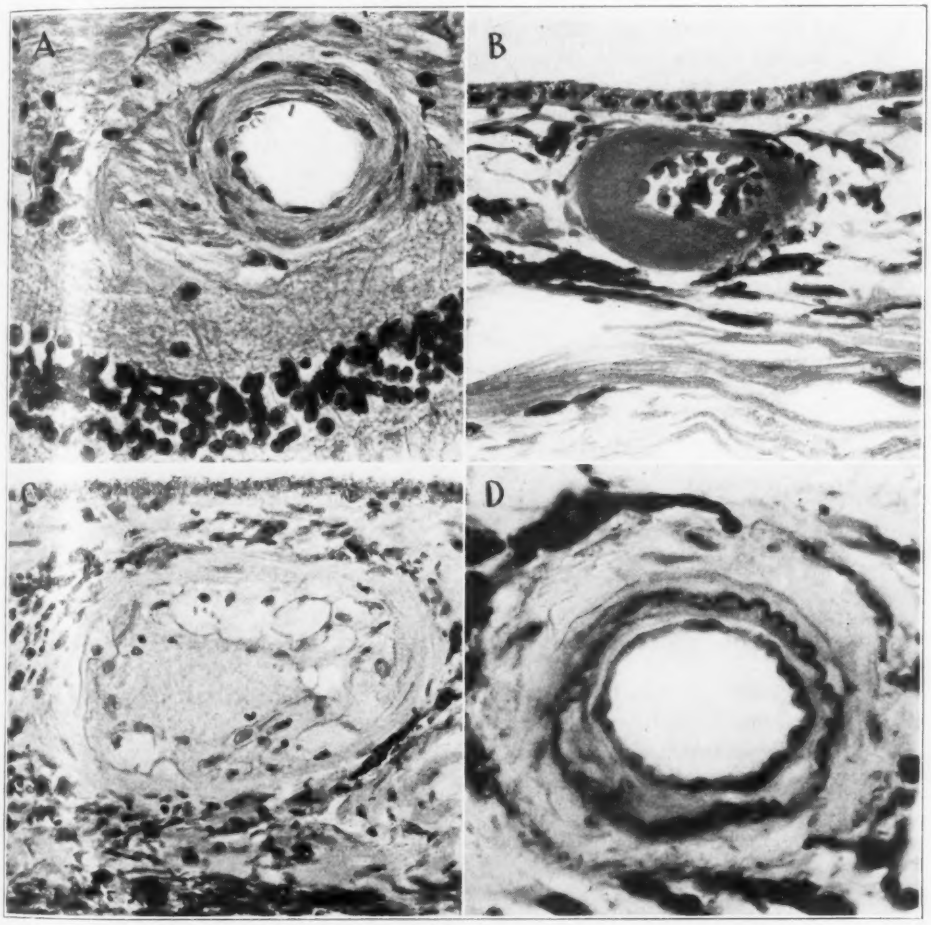

Fig. 3.—*A*, section of a retinal arteriole of a patient with malignant hypertension (case 2), showing pronounced medial hypertrophy (hematoxylin and eosin; × 365). *B*, section of a choroidal arteriole of a patient with malignant hypertension (case 11), showing hyalinization of entire wall (hematoxylin and eosin; × 365). *C*, section of a choroidal arteriole of a patient with malignant hypertension (case 1), showing infiltration of the wall with fat (hematoxylin and eosin; × 275). *D*, section of a choroidal arteriole of a patient with malignant hypertension (case 7), showing thickening and fragmentation of the elastic lamina (elastin H; × 760).

hemorrhages. The latter tended to spread along the fibers; hemorrhages that occurred in the deep layers were usually punctate and localized. Only a few hemorrhages were large enough to involve the whole thickness of the retina.

Albuminous exudates were almost entirely confined to the outer reticular layer, only occasionally spreading into the nuclear layers. They were sometimes surrounded by a rim of scavenger cells. A few of the latter were seen in the nuclear layers, but usually they were in the outer reticular layer, either singly or in clumps, which were of the same size and shape as the albuminous exudates.

Areas of fusiform degeneration of the nerve fiber layer were present in more than half the cases.

Subretinal edema, of the type described by Koyanagi [18] as typical of cases of chronic nephritis, was seen in 7 cases. This consisted of a

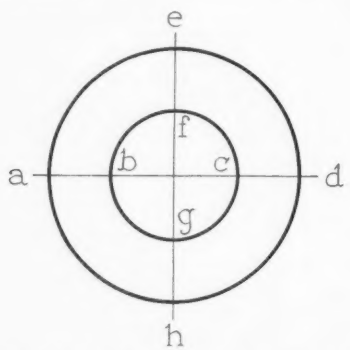

Fig. 4.—A cross section of a small artery or an arteriole, showing measurements on which the wall-lumen ratio is based.

collection of fluid adjacent to the optic nerve, raising the layer of rods and cones from the pigment epithelium.

Proliferation of the pigment cell layer was seen in only 4 cases and occurred as small knots of cells usually located in the peripheral portion of the retina.

The layer of rods and cones was notable for the fact that it was almost invariably normal.

(*c*) Measurement of Wall-Lumen Ratio: The procedure used by Kernohan was followed. Arterioles of 25+ to 120 microns in diameter, which had been cut at right angles to their course, were measured with a Bausch and Lomb micrometer. The manner of obtaining the wall-lumen ratio is illustrated in figure 4. The average [23] thickness of the

23. By "average" is meant the arithmetic mean of the total number of observations in each group.

wall, determined by averaging *a-b, c-d, e-f and g-h,* was divided into the average diameter of the lumen obtained by averaging *b-c* and *f-g.* In an effort to establish accurate ratios in each case, as many arterioles as were suitable were measured. The number measured varied greatly from case to case (table 6). In 3 controls and in 1 case of malignant

TABLE 6.—*Number of Arterioles Measured*

	Per Case	Total
Control retinal arterioles	1 - 7	16
Control choroidal arterioles	6 - 37	139
Hypertensive retinal arterioles	2 - 41	167
Hypertensive choroidal arterioles	7 - 74	410

TABLE 7.—*Summary of Wall-Lumen Ratios in Control Cases*

Retina		Choroid	
Observations	Average Ratio	Observations	Average Ratio
7	6.2	6	6.5
2	4.5	18	8.4
0	...	9	7.0
0	...	25	6.6
0	...	27	6.7
1	4.8	17	7.1
6	7.0	37	8.1
16*	5.6†	139*	7.2†

* This number represents the total.
† This number represents the average for all cases.

TABLE 8.—*Summary of Wall-Lumen Ratios in Cases of Malignant Hypertension*

	Retina		Choroid			
Case	Observations	Average Ratio	Observations	Average Ratio	Age of Patient, Yr.	Duration from Onset of Symptoms
1	23	2.8	17	1.24	55	5 yr. 9 mo.
2	8	2.4	7	0.9	50	3 mo.
3	41	1.8	18	1.6	65	7 mo.
4	4	1.2	13	1.5	50	1 yr.
5	4	2.6	29	2.4	22	7 mo.
6	22	3.2	74	3.3	29	9 mo.
7	0	...	10	1.2	55	5 yr.
8	16	3.1	68	3.2	32	5 mo.
9	2	5.0	12	4.5	32	2 mo.
10	4	2.2	60	2.6	33	9 mo.
11	15	3.0	24	5.4	51	1½ yr.
12	2	6.0	37	6.5	63	2 yr.
13	11	2.8	7	2.4	53	6 mo.
14	8	3.4	16	6.3	53	6 mo.
15	7	3.2	18	3.7	43	5 wk.
Total or average	167	3.1	410	3.2		

hypertension no retinal arterioles were found which were suitable for measurement. When the number of retinal arterioles measured was small, this was due to the great frequency with which these exceedingly thin-walled vessels are distorted in sectioning.

These measurements show the average wall-lumen ratio of the retinal arterioles of the normal controls (table 7) to be 1 : 5.6, with variations

of 1:4.5 to 1:7.0. This is in distinct contrast to the cases of malignant hypertension (table 8), in which the average ratio was 1:3.1, with variations of 1:1.2 to 1:6.0 (figs. 5 and 6). Unfortunately, the number of normal retinal arterioles measured was too small to be considered

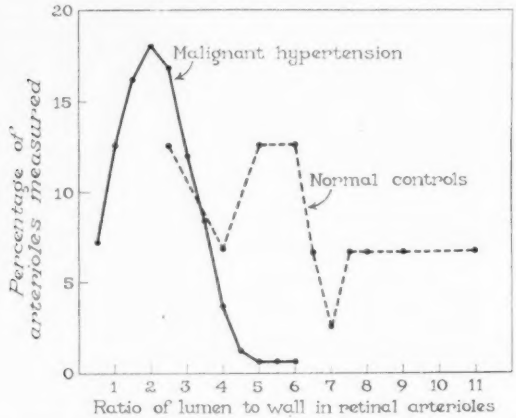
Malignant hypertension
Normal controls
Percentage of arterioles measured
Ratio of lumen to wall in retinal arterioles

Fig. 5.—The frequency distribution of the ratio of wall to lumen in retinal arterioles.

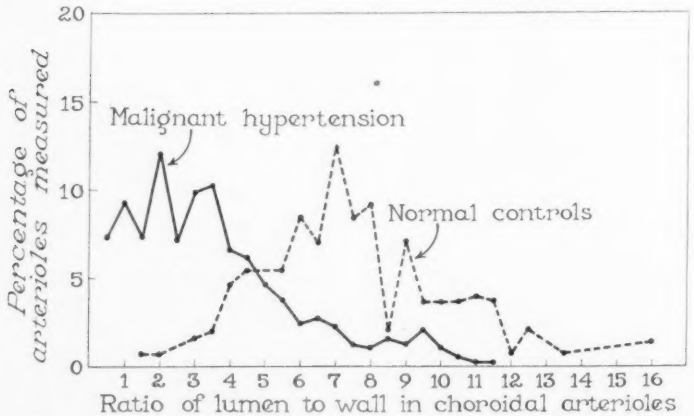
Malignant hypertension
Normal controls
Percentage of arterioles measured
Ratio of lumen to wall in choroidal arterioles

Fig. 6.—The frequency distribution of the ratio of wall to lumen in choroidal arterioles.

statistically significant. The choroidal arterioles produced similar findings. The average ratio for normal choroidal arterioles was found to be 1:7.2, with variations from 1:6.5 to 1:8.4. For the choroidal arterioles of patients who had malignant hypertension, on the other hand, the average ratio was 1:3.2, with variations of 1:0.9 to 1:6.5.

COMMENT

From the foregoing material it is evident that in the eyes, as in most other organs, malignant hypertension is accompanied with pronounced alteration of the structure of the arterioles. I was unable to demonstrate any relationship between the arterioles and the other retinal lesions. In fact, several cases in which there were great numbers of retinal hemorrhages and exudates were remarkable for the absence of any arteriolar disease except a little medial thickening. If the other retinal lesions in the eye in cases of this disease are the result of arteriolar disease, the causal relationship remains to be demonstrated.

It is noteworthy that intimal proliferation, seen so commonly in the choroidal arterioles, was seen only rarely in the retinal arterioles in my cases. This may have been due to the fact that the choroidal arterioles observed were, for the most part, of larger caliber than those seen in the

TABLE 9.—*Summary of Wall-Lumen Mean Ratios*

Organ	Wall-Lumen Ratio		Per Cent Reduction from Normal Mean of Wall-Lumen Ratio
	Control	Malignant Hypertension	
Spleen [5c]	1.32	1.04	21
Thyroid gland [5b]	1.68	1.30	23
Kidneys [5a]	1.80	0.7	61
Pectoral muscle [6]	2.0	1.1	45
Heart [5d]	2.08	1.88	10
Gastrointestinal tract [5c]	2.13	1.14	46
Liver [5c]	2.31	1.14	50
Pancreas [5c]	2.45	1.24	49
Brain [5e]	3.5	1.70	51
Retina	5.6	3.1	45
Lungs [24]	3.5 - 7.0 (25μ) (115μ)*		
Choroid	7.2	3.2	56

* This is the outside diameter of the arteriole.

retina. However, since such changes were absent even in the largest retinal arterioles, this may not be the whole answer.

The last column of table 9 serves to emphasize the fact that the degree of arteriolar disease in malignant hypertension varies considerably in different organs. The greatest change occurred in the kidneys, in which the mean wall-lumen ratio was reduced by 61 per cent. Other organs which showed conspicuous change were: the choroid, 56 per cent; the brain, 51 per cent; the liver, 50 per cent, and the pancreas, 49 per cent. The heart, the spleen and the thyroid gland showed only slight changes of 10 to 23 per cent. These observations serve again to emphasize the diffuseness of the arteriolar disease in this type of hypertension.

SUMMARY AND CONCLUSIONS

The wall-lumen ratios of the retinal and choroidal arterioles measured in this series are greater than those of the arterioles measured in any

other organ studied by this method except the lung.[24] This is in accord with the work of Coats,[9] who stated that the walls of arterioles observed in the eye are thinner than those in other organs.

The wall-lumen ratios of arterioles are definitely decreased in cases of malignant hypertension.

The most common manifestations of arteriolar lesions seen were medial hypertrophy and intimal proliferation. The choroidal vessels were much more affected than the retinal. Hyalinization of part or all of the arteriolar wall was seen frequently. Acute necrosis was seen occasionally.

No relationship was demonstrated between the arteriolar disease and other retinal lesions.

REPORT OF CASES

CASE 1.—A married white woman, 55 years of age, came to the Mayo clinic on Dec. 6, 1923, complaining of shortness of breath. She had been well until five years before admission, when recurrent bouts of shortness of breath, swelling of the ankles and nocturia began.

The past and the family histories contributed nothing of significance.

The systolic blood pressure was 210 mm. of mercury and the diastolic 160. A funduscopic examination revealed the retinopathy of malignant hypertension. The heart measured 3 by 13 cm., with a heaving precordial impulse and accentuation of the second aortic sound. There were rales at the bases of both lungs and pitting edema of the ankles. There was sclerosis of the peripheral arteries.

After two weeks of treatment in the hospital, the patient went home feeling well but returned on Sept. 14, 1924, complaining that for three months she had suffered from progressive dyspnea, weakness, edema, palpitations and periods of disorientation. Examination revealed the same conditions as before, plus anasarca. She failed rapidly and died on the fifth day after her admission to the hospital.

CASE 2.—A white man, 50 years of age, was admitted to the clinic on Nov. 13, 1924, complaining of shortness of breath and a cough. He had felt well until two and a half months before admission, when sudden attacks of dyspnea began, accompanied with a cough productive of frothy sputum. There had also been nervousness, blurred and dim vision and progressive loss of weight. During the week previous to admission there had been repeated attacks of vomiting, as well as swelling of the ankles.

The patient was cyanotic and orthopneic. The systolic blood pressure was 220 mm. of mercury and the diastolic 140. There were dulness on percussion and rales at the bases of both lungs, and the heart measured 4 by 14 cm. The abdomen was tensely distended, with the edge of the liver 6 cm. below the costal margin, and there was severe pitting edema of the legs and the back. The optic fundi showed the retinopathy of malignant hypertension.

The course was marked by progressive renal failure, uremic coma and death on the patient's fifteenth day in the hospital. A pericardial friction rub was heard on the day before the patient died.

CASE 3.—A white merchant, 65 years of age, was brought to the clinic on Aug. 11, 1925, because seven months before this time he had had a sudden

24. Kaump, D. H., and Dry, J. J.: Pulmonary Arteriolar Sclerosis: A Clinicopathologic Study, Arch. Int. Med. **61**:1-18 (Jan.) 1938.

"general breakdown," marked by extreme weakness and loss of memory. His blood pressure at that time was stated to have been 250 to 280 mm. of mercury. Progressive mental deterioration, bouts of delirium, noticeable dyspnea and visual failure had developed. At times the patient had passed blood in his stools.

The patient was hyperactive, dyspneic and confused. The optic fundi presented the retinopathy of malignant hypertension. The heart measured 3.5 by 11.5 cm., and auricular fibrillation was present. Systolic and diastolic murmurs were heard in the mitral area, and a systolic murmur was heard in the aortic area. Rales were heard at the bases of both lungs.

The course was marked by progressive pulmonary congestion, coma and death on the patient's eighth day in the hospital.

CASE 4.—A white man, 50 years of age, was admitted to the hospital on Jan. 27, 1927, because of severe dyspnea. His illness had begun one year before with nocturnal attacks of "asthma," followed by increasing urinary frequency, nocturia, dyspnea on effort, swelling of the ankles and abdominal distention.

The patient was orthopneic and had severe edema of the legs and the back. The systolic blood pressure was 220 mm. of mercury and the diastolic 140. The optic fundi showed the retinopathy of malignant hypertension. Sclerosis of the peripheral arteries was graded 2. The heart measured 3 by 15 cm., and the pulmonic second sound was accentuated. Rales were heard at the bases of both lungs, and there was fluid in the abdomen.

The course was marked by gradually progressive cardiac and renal failure, with terminal convulsions, fibrillary muscular twitching, Cheyne-Stokes respirations, coma and death five weeks after the patient's admission to the hospital.

CASE 5.—A white farmer, 22 years of age, came to the clinic on May 5, 1933, complaining that six months previously urinary frequency and nocturia had developed, followed by swelling of the ankles, fatigue and dimness of vision.

The systolic blood pressure was 244 mm. of mercury and the diastolic 162. Funduscopic examination showed the retinopathy of malignant hypertension, and the heart was slightly enlarged.

The patient went home, but four weeks later he was brought back to the hospital with the story that one week previously scotomas, periods of loss of all except central vision and severe headaches had begun. On the day of admission he had suddenly collapsed and passed into coma.

Physical examination revealed a comatose patient with Cheyne-Stokes breathing. There were divergent strabismus and unequal pupils, and the extremities were spastic on the right side. The clinical diagnosis was cerebral hemorrhage. The patient died suddenly, three hours after his admission to the hospital.

CASE 6.—A white clerk, 29 years of age, came to the clinic on Oct. 4, 1933, because nine months previously blurred vision and a blood pressure of "200" had developed, followed by severe headaches in the morning, vomiting spells, progressive loss of weight, nocturia, fatigue and palpitations.

The systolic blood pressure was 240 mm. of mercury and the diastolic 150. The optic fundi showed the retinopathy of malignant hypertension. The heart measured 3 by 10 cm.; the aortic second sound was accentuated, and there was an aortic systolic murmur. Moist rales were heard at the bases of the lungs. Sclerosis of the peripheral arteries was graded 3.

The course was marked by small urinary output (120 to 650 cc. daily), stupor and coma, with death occurring on the twelfth day after the patient's admission to the hospital. A precordial friction rub appeared four days before the patient died.

CASE 7.—A white man, 55 years of age, came to the clinic on Aug. 21, 1934. He stated that he had been well until five years before, when, because of nocturia and dyspnea, he had consulted a physician, who found him to have hypertension. During the past year, because of fulness in the neck, tremor, increasing nervousness, loss of weight and an elevated basal metabolic rate, he had been thought to have goiter. There had been no response to treatment with iodine. Six months previously, the vision in his right eye had become suddenly clouded, after which he had progressive weakness, dyspnea, cough and substernal pain on effort.

The patient was orthopneic and hyperactive, and the breath bore a urinous odor. There was considerable tremor of the hands. Both lobes of the thyroid gland were enlarged and nodular. The heart measured 3 by 12 cm., and there was a gallop rhythm. The aortic second sound was greatly accentuated, and there was an aortic systolic murmur. There were rales at the bases of both lungs, and the liver extended 6 cm. below the costal margin. The optic fundi showed the retinopathy of malignant hypertension.

The patient exhibited progressive cardiorenal failure and passed into coma. Cheyne-Stokes breathing developed, and he died on the sixth day in the hospital.

CASE 8.—A white man, 32 years of age, who came to the clinic on Feb. 11, 1935, had been well until five months previously, when nocturia, gross hematuria and pain in both loins had begun, followed by severe headaches and episodes of vomiting. For two and a half months vision in both eyes had been much impaired. Three weeks previously, the patient had had a generalized convulsion lasting fifteen minutes, following which he had had a persistent internal squint and progressive weakness.

The patient was weak and sallow. The systolic blood pressure was 240 mm. of mercury and the diastolic 140. The right eyeball was turned inward, and the fundi showed the retinopathy of malignant hypertension. The heart was enlarged, and the aortic second sound was greatly accentuated.

The patient failed rapidly and died in uremic coma nine days after his admission to the hospital.

CASE 9.—A white farmer, 32 years of age, came to the clinic on Nov. 14, 1938. Morning headaches of a severe type and nocturia had begun two months previously, followed by progressive visual failure, nausea, vomiting, diarrhea, puffiness of his face and palpitations.

The systolic blood pressure was 220 mm. of mercury and the diastolic 130. Sclerosis of the peripheral arteries was graded 3. The heart measured 3.5 by 11 cm., and there was a heaving precordial murmur. Funduscopic examinations showed the retinopathy of malignant hypertension.

The patient failed progressively, became comatose and died on the eighth day in the hospital.

CASE 10.—A Negro, 33 years of age, came to the clinic on Jan. 2, 1940, complaining that nine months before this time severe fronto-occipital morning headaches had begun, followed by blurred vision, nausea and vomiting, easy fatigue, dyspnea on effort and progressive loss of weight. He had been known for six months to have hypertension and albuminuria.

The patient was thin and sickly looking, and his breath smelled of urine. The systolic blood pressure was 240 mm. of mercury and the diastolic 160. The left border of the heart measured 11 cm.; the aortic second sound was greatly accentuated, and gallop rhythm was present. Sclerosis of the peripheral arteries was graded 3. Funduscopic examination revealed the retinopathy of malignant hypertension.

The patient's course was marked by progressive cardiorenal failure, and he died on the twelfth day in the hospital.

CASE 11.—A white man, 51 years of age, came to the clinic on Feb. 4, 1942. He stated that he had been well until one and a half years before, when he had experienced a sudden attack of pain in the left flank extending to the groin, dysuria and urinary frequency. After two weeks of constant pain, nephrectomy had been done on the left side. He was told that he had had an aneurysm of the renal artery and that he had hypertension. He had been weak ever since this operation. In the five months before his admission to the clinic severe occipital headaches, nocturnal attacks of dyspnea, swelling of the ankles, vomiting and clouded sensory perception had developed. Two weeks previously he had had a sudden attack of unconsciousness lasting four hours, followed by persistent clouding of vision.

The systolic blood pressure was 220 mm. of mercury and the diastolic 120. The heart was enlarged, and the pulmonic second sound was greater than the aortic second sound. Sclerosis of the peripheral arteries was graded 3. The optic fundi showed the retinopathy of malignant hypertension.

The patient had repeated bouts of severe headache, accompanied with nausea and vomiting. Two weeks after his admission to the hospital, he suddenly passed into coma and had several convulsions. Right hemiplegia developed. He died fifteen days after admission.

CASE 12.—A white man, 63 years of age, came to the clinic on April 21, 1943. He stated that he had been well until two years before, when he noted a sudden diminution of visual acuity followed by gradually increasing weakness and impairment of memory. For six weeks, he had had severe headaches in the morning and for two weeks he had stumbled frequently in walking.

The systolic blood pressure was 260 mm. of mercury and the diastolic 158. The patient was mildly ataxic. The heart was enlarged, and the pulmonic second sound was greater than the aortic second sound. Sclerosis of the peripheral arteries was graded 2. Examination with the funduscope revealed the retinopathy of malignant hypertension.

Three days after hospitalization the patient became disoriented. This was followed by increasing tachycardia, Cheyne-Stokes breathing, rise of temperature to 102 F. and death on the tenth day.

CASE 13.—A white man, 53 years of age, was stuporous when he was admitted to the hospital on Sept. 1, 1943. Although it was stated that two years before his blood pressure had been found to be "200+," he had had no symptoms until six months before, when progressive weakness and dyspnea had begun. For three months there had been increasing edema of the legs and some blurring of vision.

The systolic pressure was 240 mm. of mercury and the diastolic 130. Pitting edema was severe in the legs and over the sacrum. There were moist rales at the bases of both lungs and dulness on percussion at the right base. The heart was enlarged, the aortic second sound was accentuated, and a gallop rhythm was heard. The liver was 4 fingerbreadths below the right costal margin, and there was sclerosis, grade 3, of the peripheral arteries. Funduscopic examination revealed the retinopathy of malignant hypertension.

The patient's course was marked by rapidly progressive cardiorenal failure, with death on the ninth day after his admission to the hospital.

CASE 14.—When a white man 53 years of age came to the clinic in April 1940 for prostatic resection, his highest blood pressure was 140 mm. of mercury

systolic and 82 diastolic. He returned on Jan. 1, 1944, stating that six months previously he had noted sudden onset of exhaustion, increasing dyspnea on effort and edema of the ankles, severe headaches in the morning, attacks of paroxysmal nocturnal dyspnea and progressive loss of weight. One month previously, because his vision suddenly blurred, he went to a physician, who found his blood pressure "250." He had vomited each morning for four days.

The patient was ashen, anxious and sickly looking. There was considerable enlargement of the heart and the aortic second sound was greatly accentuated. A few moist rales were heard at the bases of the lungs. The optic fundi showed the retinopathy of malignant hypertension.

The patient's course was marked by progressive cardiorenal failure with increasing weakness, Cheyne-Stokes breathing and pulmonary edema. He died fourteen days after his admission to the hospital.

CASE 15.—A white man, 43 years of age, came to the clinic on Dec. 10, 1943. In the previous year he had lost 22 pounds (10 Kg.) but otherwise felt well until five weeks before coming to the clinic, when he noted painless hematuria, dyspnea on effort, severe headaches in the morning and aching lumbar pain. For two weeks his vision had been failing, and he had had some swelling of the ankles and, for the same period, aching in the right groin and testicle.

The systolic blood pressure was 205 mm. of mercury and the diastolic 135. There was considerable tortuosity of the temporal arteries. The heart was enlarged to the left. Examination with the funduscope revealed the retinopathy of malignant hypertension. When a simple roentgenogram of the abdomen showed calculi in the left kidney, an excretory urogram was attempted. Neither kidney excreted the dye in visible amounts.

Twelve hours after this procedure, the patient suddenly passed into a coma. It was the opinion of a neurologist that the patient had had a cerebral hemorrhage. He died two days later.

CARDIAC MUSCLE

Further Studies; Investigation of Chemical Changes in Myocardial Insufficiency with Special Reference to Adenosinetriphosphate

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DURING the past decade chemical studies have been made on the human heart by workers from several laboratories in an effort to correlate heart failure with known facts of muscle chemistry. From these studies has come a consistent agreement among all published data that creatine is usually decreased in the failing heart. Total phosphorus and acid-soluble phosphorus have likewise been found to be decreased,[1] and most workers have found a lowered potassium.

To investigate further the chemical changes associated with myocardial insufficiency, Mangun and Roberts [2] studied acid-soluble phosphorus compounds of the dog's heart in aortic insufficiency. No losses were observed in the early stages, but in 2 dogs allowed to progress into the late stages of cardiac failure (approximately one year later) a marked decrease was noted in the adenosinetriphosphate and phosphocreatine content of the left ventricle. These findings made it desirable to investigate the adenosine compounds present in the failing

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From the Department of Biochemistry, School of Medicine, Western Reserve University. The material for this study was obtained through the cooperation of the Department of Pathology, Western Reserve University.

A preliminary report of this work was presented before the American Society of Biological Chemists, 1940. Mangun, G. H., and Myers V. C.: Purine Content of Human Cardiac and Voluntary Muscle, J. Biol. Chem. **133**:1xii, 1940.

1. (*a*) Wilkins, W. E., and Cullen, G. E.: Electrolytes in Human Tissue: A Comparison of Normal Hearts with Hearts Showing Congestive Heart Failure, J. Clin. Investigation **12**:1063, 1933. (*b*) Decherd, G. M., Jr., and Blum, G. E., Jr.: Phosphorus Fractions in Human Heart Muscle, Proc. Soc. Exper. Biol. & Med. **38**:341, 1938. (*c*) Mangun, G. H.; Reichle, H. S., and Myers, V. C.: Further Studies on Human Cardiac and Voluntary Muscle: Possible Implications of Changes in the Creatine, Phosphorus and Potassium Content with Special Reference to Heart Disease, Arch. Int. Med. **67**:320 (Feb.) 1941. (*d*) Herrmann, G., and Decherd, G. M., Jr.: The Chemical Nature of Heart Failure, Ann. Int. Med. **12**: 1233, 1939.

2. Mangun, G. H., and Roberts, J. T.: Unpublished observations.

human heart. Since adenosinetriphosphate and related compounds break down rapidly after death, it was necessary to devise a technic suitable for the estimation of total acid-soluble purines in such tissues.

Several methods were studied, but only one proved to possess suitable characteristics of specificity, accuracy and sensitivity to warrant use with small samples of tissue. The method consists essentially in the precipitation of purines in a hydrolyzed trichloroacetic acid extract of tissue with copper bisulfite and the estimation of the nitrogen content of the precipitate. Since the purines present are undergoing varying degrees of deamination to oxypurines, it is also necessary to convert unchanged amino purines to oxypurines. Nitrous acid deamination was employed for this purpose. The final method as used in the present series of determinations is as follows:

METHOD

For the determination of oxypurine nitrogen a sample of tissue weighing about 1 Gm. is transferred to a mortar and ground with ten times its weight of 5 per cent trichloroacetic acid, washed and filtered. An aliquot of the filtrate containing not less than 0.2 mg. of nitrogen (10 cc. or more) is transferred to a conical centrifuge tube. Enough ten times normal sulfuric acid is added to make the solution normal, and this is followed by 2 to 3 drops of 1:2 solution of sodium nitrite. The solution is placed in a boiling water bath for one hour to remove the trichloroacetic acid and excess nitrous acid, after which it is cooled, and a drop of phenolphthalein added and neutralized with sodium hydroxide to a faint pink. It is then replaced in the boiling water bath, and 0.4 cc. of saturated solution of sodium bisulfite is added, followed by 0.6 cc. of 10 per cent solution of copper sulfate for each 10 cc. of solution. Heating is continued for several minutes until the precipitate becomes dark brown. It is then cooled and centrifuged. The precipitate is washed with 2 cc. portions of boiling water, the precipitate being broken with a stirring rod and centrifuged after each washing. The nitrogen content of the precipitate is now determined by the micro-Kjeldahl method of Kerr.[3] If total extractive purine nitrogen is desired, addition of sodium nitrite is omitted. Other determinations were carried out as described in an earlier paper.[1c]

In our earlier studies on normal and pathologic human hearts a large number of the calculations were also made on dry fat-free tissue. Some added information may be secured in this way, but significant changes were always evident in the analyses calculated on a wet basis. On this account the analyses given in the present paper are reported only on a wet basis.

RESULTS OF EXPERIMENTS

The recovery of oxypurine nitrogen from known solutions and after addition to trichloroacetic acid extracts of muscle is shown in table 1. The data demonstrate that complete conversion of amino purine to oxy-

3. Kerr, S. E.: The Determination of Purine Nucleotides and Nucleosides in Blood and Tissues, J. Biol. Chem. **132**:147, 1940.

purines has been obtained with nitrous acid without loss of oxypurine and that quantitative recoveries of added purines are obtained in tissue extracts.

The effects of autolysis on the purine content of cardiac muscle are shown in table 2. Essentially no change in oxypurine nitrogen occurs in samples at 3 to 5 C. for forty-eight hours although there is a progressive decrease in the total purine nitrogen during the first twenty-four hours to a value only slightly higher than the oxypurine content.

TABLE 1.—*Recovery of Oxypurines from Pure Solutions and Trichloroacetic Acid Extracts of Muscle (Average of Triplicate Determinations)*

Purine Added	Oxypurine Nitrogen in Original Sample, Mg.	Oxypurine Added, Mg.	Total Oxypurine Found, Mg.	Recovery, Percentage
Adenine	0	0.357	0.355	99.5
Hypoanthine	0	0.496	0.497	100.2
Guanine	0	0.459	0.465	101.1
Xanthine	0	0.384	0.386	99.6
Adenine added to skeletal muscle extract	0.388	0.143	0.478	99.4
Adenine added to human heart extract	0.191	0.143	0.339	101.8
Adenine added to dog heart extract	0.172	0.143	0.314	99.4

TABLE 2.—*The Effect of Autolysis on Cardiac Muscle Purine Nitrogen* (Mg. of Purine Nitrogen per Hundred Grams of Muscle)*

Purines Determined	Hours Post Mortem			
	2 Hr.	12 Hr.	24 Hr.	48 Hr.
Total extractive purine nitrogen	41.2	37.1	36.5	36.8
Oxypurine nitrogen	34.4	35.1	33.9	34.7

* Stored in icebox at 3 to 5 C.

TABLE 3.—*Average Purine Nitrogen Content of Human Cardiac and Voluntary Muscle in Ten Cases (Mg. per Hundred Grams of Muscle)*

	Total Extractive Purine Nitrogen	Oxypurine Nitrogen	Amino Nitrogen
Left ventricle	38.0	34.5	3.5
Right ventricle	25.2	22.3	2.9
Pectoralis major	34.3	31.1	3.2

Data on 10 miscellaneous cases in which both total extractive purine nitrogen and oxypurine nitrogen were determined in the left and the right ventricle and the pectoralis major are presented in table 3. In most cases it was found that about half of the total purines were deaminized. For individual cases this ranged from 35 to 85 per cent, if all nitrogen lost by treatment with nitrous acid is assumed to arise from the deamination of adenine.

Analytic observations at necropsy in a series of 24 cases, in which oxypurine nitrogen, creatine and total acid-soluble phosphorus were determined, are summarized in table 4. The following deductions seem warranted:

The adenine content (calculated on the basis of oxypurine nitrogen) of the left ventricle bears the same approximate relationship as the creatine and phosphorus content and are probably due to the same cause, namely, a relatively higher percentage of muscle tissue in the left ventricle per unit weight of tissue.

The adenine content of voluntary muscle is approximately the same as that of the left ventricle. Creatine, however, is nearly twice as high in voluntary muscle as it is in the myocardium of the left ventricle.

In 5 of 6 cases of myocardial insufficiency, the purine content of the left ventricle was lower than that observed in the 18 remaining cases in which death was attributed to other causes. In the 1 case in which the

TABLE 4.—*Average Oxypurine Nitrogen (Calculated as Adenine), Creatine and Total Acid-Soluble Phosphorus Content of Human Cardiac and Voluntary Muscle in Different Conditions (Mg. per Hundred Grams)*

		Left Ventricle			Right Ventricle			Pectoralis Major		
	No. of Cases	Adenine	Creatine	Total Acid-Soluble Phosphorus	Adenine	Creatine	Total Acid-Soluble Phosphorus	Adenine	Creatine	Total Acid-Soluble Phosphorus
Entire series.....	24	86	205	106	54	152	74	77	388	148
Heart failure.....	6	72	161	91	54	128	67	71	344	129
Tuberculosis.....	5	87	225	117	56	162	78	74	422	161
Pneumonia.....	8	90	222	110	48	160	75	78	386	145
Miscellaneous.....	5	91	311	107	63	161	78	87	406	163

purine content of the left ventricle was essentially normal, the purine content of the right ventricle was substantially lowered. In some cases of pneumonia, but not all, the right ventricle appears to be chemically deficient. This suggests that the right ventricle may become fatigued in those conditions involving the lungs to such a degree as to cause failure of the right side of the heart. Findings with regard to creatine and total acid-soluble phosphorus are in essential agreement with results previously reported.[4]

COMMENT

The method presented in the paper for the determination of purines was not further investigated for specificity. However, a high degree of

4. Myers, V. C., and Mangun, G. H.: Some Chemical Observations on the Human Heart in Health and Disease, J. Lab. & Clin. Med. **26**:199, 1940. Myers, V. C.: Some Chemical Changes in the Myocardium Accompanying Heart Failure, Bull. New York Acad. Med. **18**:303, 1942.

specificity has previously been demonstrated for the copper bisulfite method of purine precipitation.[5] It was noted that when the nitrous acid deamination was applied to tissue extracts, autolysis resulted in no change in oxypurine nitrogen within forty-eight hours after death. In the absence of nitrous acid, the total purine nitrogen decreased during the first twelve hours to a value of approximately 2 mg. per hundred grams higher than the oxypurine value, and dropped no further within the forty-eight hour observation period. This may be due to the precipitation of a small amount of some other nitrogenous compound which is destroyed by treatment with nitrous acid.

It is probable, but not proved, that most of the acid-extractable purines found in muscle tissue originate from the hydrolysis of adenosinetriphosphoric acid and related compounds.

A recent report by Stoner and Green [6] indicates that tissue damage releases adenosine compounds sufficiently to cause a noticeable rise in the adenosine equivalent of the blood. This fact may be related to the decreases in purines observed in the heart in myocardial insufficiency.

A recent paper by Palladin [7] on the biochemistry of muscle training summarizes the results of a series of studies on the effects of muscle training and fatigue on voluntary muscle. The Kiev group demonstrated that training increased the concentrations of various muscle constituents believed to be intimately associated with transfer of muscle energy and with cell respiration, while fatigue adversely affected the untrained muscle tissue to a far greater degree than the trained. It is probable that our observations on the heart are fundamentally related to the same phenomena and that the changes observed are directly related to a decrease in the chemical efficiency of the heart arising either from fatigue due to overwork or from tissue anoxia, as suggested by Wearn.[8]

The observations of the Kiev group on the poor results of training in animals on vitamin C-free and on thiamine-free diets also emphasize a point of both practical and theoretic significance—that unless favorable nutritional conditions are created, the ability of muscle to withstand fatigue and to respond to increased energy demands is poor.

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5. Hitchings, G. H., and Fiske, C. H.: The Determination of the Purines, J. Biol. Chem. **140**:491, 1941.

6. Stoner, H. B., and Green, H. N.: Further Observations on the Adenosine Equivalent of the Blood of Rabbits Following Lethal Forms of Tissue Injury, J. Path. & Bact. **57**:337, 1945.

7. Palladin, A. V.: The Biochemistry of Muscle Training, Science **102**:576, 1945.

8. Wearn, J. T.: Morphological and Functional Alterations of the Coronary Circulation, Bull. New York Acad. Med. **17**:754, 1941.

SUMMARY

A method is presented for the estimation of total acid-soluble purines and of oxypurines in biologic material which involves hydrolysis of purine compounds, deamination with nitrous acid, precipitation with copper bisulfite and estimation of the nitrogen content of the precipitate.

The acid-extractable purine content of the left ventricle, calculated as adenine, is decreased in myocardial insufficiency. Lowered concentrations of purine were also observed in the myocardium of the right ventricle in some, but not all, cases of pneumonia.

Progress in Internal Medicine

INFECTIOUS DISEASES

Twelfth Annual Review of Significant Publications

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THE RESULTS of continued research on antibiotic agents and their practical application hold the chief interest in the field of infectious diseases. Much knowledge has accrued concerning the value of penicillin, streptomycin and other agents when used in the treatment of certain infections and their lack of effect when used in the treatment of others. Intensive investigation of the chemical structure of antibiotics and development of better methods for their commercial production are in progress. The use of penicillin to combat many serious infections, such as the bacterial pneumonias, infections with hemolytic streptococci and subacute bacterial endocarditis, has brought about a great reduction in their incidence and mortality rate. The mortality from degenerative cardiac, renal and other diseases has also declined as a result of the control of incidental infections, which commonly cause death in such patients.[1] This decline, however, has been continuous for many years. No doubt it has been speeded by modern methods of prevention and treatment. Further reduction of the incidence and the mortality rate of chronic cardiovascular-renal and other degenerative diseases may be anticipated in the future from the present control of certain infections which give rise to such diseases.

Many advances in knowledge have come from extensive investigation of diseases affecting the armed forces, particularly epidemic infections of the respiratory tract, hepatitis, malaria and exotic diseases. There have also been alarming developments pertaining to the possibilities of future biologic warfare. Although assurance was given in 1943 [2] that there were insurmountable difficulties in the way of the successful use of infectious agents as offensive weapons, it now is evident that confidence was not actually so great.[3] While biologic warfare is still

From the Jefferson Medical College and Hospital.

1. Large Decline in Mortality from Degenerative Diseases, Statist. Bull. Metrop. Life Insur. Co. **27**:5-8 (March) 1946.

2. Feasibility of Bacterial Warfare, editorial, J. A. M. A. **122**:810-811 (July 17) 1943.

3. Biologic Warfare, editorial, J. A. M. A. **130**:349 (Feb. 9) 1946.

largely theoretic, since no practical application has been made, secret but active investigation on a large scale has been conducted to forestall any surprise attacks and to develop protective and aggressive measures with respect to contagious diseases of animals, plants and man. The organization of the project and its objectives are described by Merck.[4]

PENICILLIN

Although the commercial output of penicillin has increased to 1.5 trillion units a month, it is only recently that domestic demand has been exceeded.[5] Despite the large supply, there were several periods during the winter when it fell short of the demand. A large amount of penicillin is wasted, and its more judicious use would do much to prevent a shortage. A committee in New York warned that penicillin should not be used for the prophylaxis and the treatment of diseases for which it is of no value, that treatment of patients should not be continued long after any effect may be expected and that oral administration of the drug should not be practiced since it requires a several-fold increase of dosage.[6] Doses giving optimal amounts in the blood are all that is needed; larger doses merely raise the amount without increasing antibacterial activity.[7] The application of silly trade names to penicillin was deprecated editorially.[8] Interesting reviews of the development of antibiotics were made by Florey[9] and by Molitor.[10] Research on antibiotics has gone on for seventy years, and the word "antibiosis" was coined in 1889.

Certain information concerning penicillin withheld during the war is now released.[11] Commercial penicillin is not a single substance but a mixture of at least four chemical types of penicillin designated as G, X, F and K, which appear in varying combination and proportion, depending on the strain of Penicillium used for harvest, on the method of preparation and on other factors. Prior to 1944 penicillin was composed

4. Merck, G. W.: Biological Welfare, Mil. Surgeon **98**:237-242 (March) 1946.

5. Production of Penicillin High Enough to Permit Export, Washington Letter, J. A. M. A. **131**:1009 (July 20) 1946.

6. Penicillin Therapy, Current Comment, J. A. M. A. **130**:414 (Feb. 16) 1946.

7. Rammelkamp, C. H., and Kirby, W. M. M.: Factors Determining the Dosage of Penicillin in the Treatment of Infections, Bull. New York Acad. Med. **21**:656-672 (Dec.) 1945.

8. Silly Names for Penicillin Products, editorial, J. A. M. A. **130**:279 (Feb. 2) 1946.

9. Florey, H. W.: The Use of Microorganisms for Therapeutic Purposes, Brit. M. J. **2**:635-642 (Nov. 10) 1945.

10. Molitor, H.: Bacterial Chemotherapy, Federation Proc. **5**:303-312 (June) 1946.

11. The Changing Character of Commercial Penicillin, Committee on Medical Research, the United States Public Health Service, and the Food and Drug Administration, J. A. M. A. **131**:271-275 (May 25) 1946.

chiefly of penicillin G or a mixture of G and F. Later, the G fraction diminished as the F and K fractions increased. It is probable that during the past three years penicillin X has been present only in a small amount. The significance of these changes lies in the fact that K penicillin is unstable, is relatively ineffective in certain infections and reduces curative power.[12] This may account partly for the apparent diminution of the rate of cures of syphilis since May 1944. Strains of group A hemolytic streptococci, pneumococci, gonococci and meningococci are from two to eight times more sensitive to penicillin X than to penicillin G.[13] Penicillin X is not absorbed as well as the G fraction when given orally.[14] A further complicating factor is the production of increasingly "pure" penicillin by the elimination of certain "impurities" which may also have therapeutic value. Penicillin as now distributed is said to contain about 95 per cent penicillin G.

Miller and Boor[15] supplement their earlier work to show that penicillin not only inhibits growth but also neutralizes the endotoxin of meningococci and gonococci. Miller and Bohnhoff[16] also demonstrated that meningococci developed resistance to penicillin while still retaining their virulence. A curious result was obtained by Carpenter and co-workers[17]: Gonococci, as would be expected, developed resistance while growing in mediums containing sulfathiazole, Rivanol (2-ethoxy-6,9-diamino-acridine lactate), Promin (sodium p,p′-diaminodiphenylsulfone-N,N′-didextrose sulfonate) and penicillin separately. But when mediums containing the first three drugs together were used, only slight resistance developed to each, and when penicillin was added to the combination, no resistance developed to any of the agents. Penicillin obviously played the most important role, probably by preventing growth during which resistance to the other drugs develops. It is hoped that a prediction made recently will not be fulfilled, namely, that owing to the wide and uncontrolled use of penicillin and the gradual

12. Coghill, R. D.; Osterberg, A. E., and Hazel, G. R.: The Relative Effectiveness of Pure Penicillin G, X and K, Science **103**:709-710 (June 14) 1946.

13. Ory, E. M.; Meads, M., and Finland, M.: Penicillin X, J. A. M. A. **129**:257-261 (Sept. 22) 1945.

14. Meads, M.; Ory, E. M., and Finland, M.: Oral Penicillin X, Science **103**:501-502 (April 26) 1946.

15. Miller, C. P., and Boor, A. K.: Protection of Mice Against Lethal Action of Gonococcal Endotoxin by Penicillin, Proc. Soc. Exper. Biol. & Med. **61**:18-20 (Jan.) 1946.

16. Miller, C. P., and Bohnhoff, M.: Studies on the Action of Penicillin: V. Virulence of Penicillin Resistant Strains of Meningococcus, Proc. Soc. Exper. Biol. & Med. **60**:356-357 (Dec.) 1945.

17. Carpenter, C. M., and others: Adaptability of Gonococcus to Four Bacteriostatic Agents, Sodium Sulfathiazole, Rivanol Lactate, Promin and Penicillin, Proc. Soc. Exper. Biol. & Med. **60**:168-171 (Oct.) 1945.

development of resistance generally among bacteria, penicillin as now prepared will eventually cease to be of value in the treatment of disease.[10]

Oral Therapy.—Penicillin given orally in about five times the usual parenteral dose accumulates in the blood in amounts large enough to control infections caused by gonococci, hemolytic streptococci and pneumococci but probably not those caused by staphylococci and meningococci, or subacute bacterial endocarditis.[18] For initiating treatment of any severe infection and for treatment in which large doses over a long period are essential, the parenteral route is preferable. Penicillin was just as satisfactory when given in capsules or dissolved in water as when administered in various combinations with buffer substances. The amount of penicillin in the blood was often greater in patients with pneumonia than in normal persons given similar amounts. Most patients with gonorrhea were cured with a daily dose of 450,000 units, given orally in divided doses, but the response was not quite so good as after full intramuscular dosage.

Pneumococcic pneumonia was satisfactorily treated [18] with an initial oral dose of 300,000 units and doses of 100,000 units every two hours thereafter until the temperature remained normal for forty-eight hours. The total dose varied between 2,500,000 and 8,500,000 units. In another group,[19] of 45 patients, only 1 death occurred. They received 200,000 units as an initial dose, followed by 50,000 units every two hours until twenty-four hours after the crisis, when the same dosage was maintained only from 8 a. m. to 10 p. m. The total doses were 750,000 units on the first day and 400,000 to 600,000 units on subsequent febrile days. Treatment usually lasted from four to seven days. In 36 patients a slight secondary rise of fever occurred during the second or the third day of treatment, but there was no evidence that a relapse had occurred. The resumption of therapy caused prompt improvement. Oral therapy in general is as effective as parenteral therapy. Oral therapy was also good in children with gonococcic vaginitis and in those with pneumonia [20] when 100,000 units was given in a capsule every three hours. No toxic symptoms resulted.

Hemolytic Streptococcic Infection.—In the experience of Meads's group,[21] if penicillin is administered parenterally early in scarlet fever and

18. Finland, M.; Meads, M., and Ory, E. M.: Oral Penicillin, J. A. M. A. **129**:315-320 (Sept. 29) 1945.

19. Bunn, P. A.; McDermott, W.; Hadley, S. J., and Carter, A. C.: The Treatment of Pneumococcic Pneumonia with Orally Administered Penicillin, J. A. M. A. **129**:320-327 (Sept. 29) 1945.

20. Ross, S.; Burke, F. G., and McLendon, P. A.: Penicillin by Mouth, J. A. M. A. **129**:327-332 (Sept. 29) 1945.

21. Meads, M., and others: Penicillin Treatment of Scarlet Fever, J. A. M. A. **129**:785-789 (Nov. 17) 1945.

treatment continued for seven days the carrier state may be eliminated and complications caused by hemolytic streptococci prevented, but the eruptive and toxic manifestations are not influenced. Another group [22] recommends that 480,000 units be given over an eight day period. Penicillin was successful in controlling scarlet fever caused by sulfonamide-fast type 17 and 19 of hemolytic streptococci. Ashley's results were similar, but he gave an injection of 50 cc. or more of human convalescent serum in addition.[23]

In the treatment of pharyngitis caused by hemolytic streptococci, penicillin given parenterally shortened the disease from 4.9 days in the untreated to 3.1 days in those treated.[24] The carrier state persisted for a week after penicillin therapy in 30 per cent of those who were treated and in all those who were untreated. Oral therapy was also effective. Spink's group [25] reports similar favorable results. Daily intramuscular injection of more than 200,000 units was needed to eliminate hemolytic streptococci from the throat more than temporarily. Penicillin did not prevent subsequent attacks of rheumatic fever. The question of the development of penicillin-fast strains of hemolytic streptococci arises, but no strains significantly resistant to penicillin were encountered.

In another study, penicillin in beeswax–peanut oil mixture injected once a day for five to seven days promptly and permanently eradicated hemolytic streptococci from the nose and the throat in 50 per cent of carriers.[26] In the other half the streptococci were reduced by 98 per cent, but relapse of the carrier state took place when treatment was stopped.

A high percentage of patients with empyema caused by hemolytic streptococci, pneumococci or staphylococci recovered without operation after being treated with penicillin.[27]

Diphtheria Carriers.—In one study [28] carriers were not freed of diphtheria bacilli by intramuscular injections of penicillin, but 23 of 31

22. Observations on the Treatment of Scarlet Fever with Penicillin, Epidemiology Unit no. 82, Am. J. M. Sc. **211**:417-420 (April) 1946.

23. Ashley, P.: The Treatment of Scarlet Fever, J. A. M. A. **130**:771-774 (March 23) 1946.

24. Keith, J. D., and others: Penicillin in Hemolytic Streptococcal Infections of the Throat, Canad. M. A. J. **53**:471-477 (Nov.) 1945.

25. Spink, W. W., and others: Sulfadiazine and Penicillin for Hemolytic Streptococcus Infections of the Upper Respiratory Tract, Arch. Int. Med. **77**: 260-294 (March) 1946.

26. Hamburger, M., and Lemon, H. M.: The Problem of the Dangerous Carrier of Hemolytic Streptococci, J. A. M. A. **130**:836-841 (March 30) 1946.

27. Brown, B., and others: Penicillin Treatment of Empyema: Report of Twenty-Four Cases and Review of the Literature, Ann. Int. Med. **24**:343-370 (March) 1946.

28. Kocher, R. A., and Siemsen, W. J.: Diphtheria Carriers Treated with Penicillin, Ann. Int. Med. **24**:883-886 (May) 1946.

persons were cleared when penicillin was given as lozenges or as a nasal spray. In carriers resistant to this form of treatment, tonsillectomy was said to result in negative cultures. The results as reported seem encouraging, but limited facilities did not permit accurate identification of the bacilli, and the cultures reported extend only to the tenth day after the beginning of treatment.

On the other hand, nasal inhalation of penicillin had no effect on the state of carrier of virulent diphtheria bacilli in Paull's [29] patients. Sixty-four per cent of the strains of diphtheria bacilli were sensitive to penicillin.

An official report [30] of a nation-wide study of the effect of penicillin as used in the treatment of 11,589 patients with syphilis has been made. The report and other pertinent ones are discussed in the "Annual Review of Syphilis" in the *Archives of Internal Medicine*.

STREPTOMYCIN

Because of the difficulties in the production of streptomycin, not many reports of its use are available for review. So far the results of the treatment of typhoid and brucellosis,[31] in which the therapy is theoretically specific, are disappointing. At present streptomycin seems to be of most value when used for certain infections of the urinary tract with gram-negative bacteria, for clearing the intestine temporarily of certain gram-negative bacteria,[31b] for tularemia,[32] for Haemophilus influenzae meningitis, for bacteremia with gram-negative bacilli and for certain infections of wounds.[33] Streptomycin was said [33a] to have

29. Paull, R., and others: Studies on the Sensitivity of Diphtheria to Penicillin, Ann. Int. Med. **24**:413-419 (March) 1946.

30. The Treatment of Early Syphilis with Penicillin, Committee on Medical Research and the United States Public Health Service, J. A. M. A. **131**:265-271 (May 25) 1946.

31. (*a*) Herrell, W. E., and Nichols, D. R.: The Clinical Use of Streptomycin: A Study of Forty-Five Cases, Proc. Staff Meet., Mayo Clin. **20**:449-462 (Nov. 28) 1945. (*b*) Reimann, H. A.; Price, A. H., and Elias, W. F.: Streptomycin for Certain Systemic Infections and Its Effect on the Urinary and Fecal Flora, Arch. Int. Med. **76**:269-277 (Nov.-Dec.) 1945.

32. (*a*) Foshay, L., and Pasternack, A. B.: Streptomycin Treatment of Tularemia, J. A. M. A. **130**:393-398 (Feb. 16) 1946. (*b*) Abel, O.: The Use of Streptomycin in Tularemia, J. Missouri M. A. **43**:167-169 (March) 1946. (*c*) Cohen, R. B., and Lasser, R.: Primary Tularemic Pneumonia Treated with Streptomycin, J. A. M. A. **131**:1126-1127 (Aug. 3) 1946. (*d*) Peterson, R. L., and Parker, R. R.: Tularemic Pneumonia: Treatment with Streptomycin, Pub. Health Rep. **61**:1231-1234 (Aug. 23) 1946. (*e*) Howe, C., and others: Streptomycin Treatment in Tularemia, J. A. M. A. **132**:195-200 (Sept. 28) 1946.

33. Streptomycin in the Treatment of Infection, Committee on Chemotherapeutics and Other Agents, J. A. M. A. **132**:4-11 (Sept. 7); 70-77 (Sept. 14) 1946.

produced an "extremely dramatic" result in a patient who presumably had H. influenzae infection of the lung, recovery occurring within eight hours after an intratracheal injection of 50 mg. Aside from the statement that H. influenzae was the predominant organism in the sputum, no proof is offered that it caused the disease in this patient or in 2 others in which recovery occurred after intratracheal injection of streptomycin. Furthermore, only slight amounts of streptomycin are absorbed when the drug is given by inhalation. Similar criticism may be applied to the report of successful parenteral treatment of a patient with pneumonia due to Friedländer's bacillus.[34] Streptomycin was used successfully for endocarditis caused by streptococci resistant to pencillin [34a] and by gram-negative bacilli.[34b] Streptomycin is said to be the most effective agent used to treat experimental tuberculosis in animals,[35] but in 34 patients [36] it seemed to have only a limited suppressive effect; there was no evidence of effective bactericidal action. Optimism is unwarranted at present. Good results are reported [37] from the treatment of an infant with tuberculous meningitis and from that of a patient with tuberculous laryngitis.[38] No effect was noted in another patient with meningitis.[31b] No effects of streptomycin were noted in 10 patients treated for cholera other than a reduction of the number of vibrios in the stools.[39] Vibrios from different patients of the same epidemic varied greatly in their resistance to streptomycin. Streptomycin

Nichols, D. R., and Herrell, W. E.: Streptomycin: Its Clinical Use and Limitations, ibid. **132**:200-205 (Sept. 28) 1946.

33a. Durant, T. M., and others: Streptomycin Therapy in Hemophilus Influenzae Pulmonary Infections, J. A. M. A. **131**:194-196 (May 18) 1946.

34. Bishop, C. A., and Rasmussen, R. F.: Klebsiella Pneumonia Treated with Streptomycin, J. A. M. A. **131**:821-822 (July 6) 1946.

34a. Priest, W. S., and McGee, C. J.: Streptomycin in the Treatment of Subacute Bacterial Endocarditis, J. A. M. A. **132**:124-126 (Sept. 21) 1946.

34b. Hunter, T. H., and Duane, R. B.: Subacute Bacterial Endocarditis Due to Gram-Negative Organisms, J. A. M. A. **132**:209-211 (Sept. 28) 1946.

35. Smith, M. I., and McClosky, W. T.: The Chemotherapeutic Action of Streptomycin and Promine in Experimental Tuberculosis, Pub. Health Rep. **60**: 1129-1138 (Sept. 28) 1945.

36. Hinshaw, H. C., and Feldman, W. H.: Streptomycin in Treatment of Clinical Tuberculosis: A Preliminary Report, Proc. Staff Meet., Mayo Clin. **20**:313-318 (Sept. 5) 1945.

37. Cooke, R. E.; Dumphy, D. E., and Blake, F. G.: Streptomycin in Tuberculous Meningitis: Reports of Its Use in a One-Year-Old Infant, Yale J. Biol. & Med. **18**:221-226 (Jan.) 1946.

38. Figi, F. A.; Hinshaw, H. C., and Feldman, W. H.: Treatment of Tuberculosis of the Larynx with Streptomycin: Report of Case, Proc. Staff Meet., Mayo Clin. **21**:127-130 (March 20) 1946.

39. Reimann, H. A., and others: Asiatic Cholera, Am. J. Trop. Med. **26**:631-647 (Sept.) 1946.

was effective in controlling experimental infections with Haemophilus pertussis [40] and Pasteurella pestis [41] in mice.

The essential features of the pharmacologic behavior of streptomycin, particularly in regard to routes of administration, amounts in the body and excretion as reported previously,[31b] have been confirmed and extended.[33]

Buggs and co-workers [43] tested the sensitivity to streptomycin of a variety of bacteria. The majority of strains of Escherichia coli, Proteus vulgaris, Aerobacter aerogenes, staphylococci and streptococci were susceptible to amounts of streptomycin in culture mediums comparable to amounts attained in the body. As in our own study,[31b] great variations in resistance to streptomycin of a given species of bacterium was found. Certain strains develop resistance to streptomycin. Experience indicates that it is questionable whether the degree of resistance of bacteria in vitro is a reliable guide to the amount needed to gain therapeutic effects in the body.[31b] Rapid development of resistance occurred in 8 patients, resulting in the failure of treatment.[43a]

With most interest focused on the effects of streptomycin on gram-negative bacteria, it comes as a surprise to learn that the majority of strains of staphylococci tested were sensitive to as little as 1 microgram of the drug. Alpha and beta hemolytic streptococci were somewhat more resistant. According to Miller and Bohnhoff,[44] meningococci and pneumococci are sensitive to streptomycin but become resistant to it much more rapidly than to penicillin when grown in mediums containing the respective antibiotic substances. Streptomycin-resistant meningococci and pneumococci were sensitive to penicillin, and penicillin-resistant strains were sensitive to streptomycin. The authors believe that penicillin and streptomycin act in different ways, since resistance to streptomycin builds up more rapidly, and abnormal morphologic changes occur in streptomycin-resistant strains but not in penicillin-resistant

40. Bradford, W. L., and Day, E.: Therapeutic Effect of Streptomycin in Experimental Murine Pertussis, Proc. Soc. Exper. Biol. & Med. **60**:324-325 (Dec.) 1945. Hegarty, C. P., and others: In Vitro and in Vivo Activity of Streptomycin Against Hemophilus Pertussis, J. Bact. **50**:651-660 (Dec.) 1945.

41. Wayson, N. E., and McMahon, M. C.: Plague: Treatment of Experimental Animals with Streptomycin, Sulfadiazine and Sulfapyrazine, J. Lab. & Clin. Med. **31**:323-332 (March) 1946. Hornibrook, J. W.: Streptomycin in Experimental Plague, Pub. Health Rep. **61**:535-538 (April 12) 1946.

42. Footnote deleted on proof.

43. Buggs, C. W., and others: The In Vitro Action of Streptomycin on Bacteria, J. A. M. A. **130**:63-67 (Jan. 12) 1946.

43a. Finland, M., and others: Development of Streptomycin Resistance During Treatment, J. A. M. A. **132**:16-21 (Sept. 7) 1946.

44. Miller, C. P., and Bohnhoff, M.: Streptomycin Resistance of Gonococci and Meningococci, J. A. M. A. **130**:485-488 (Feb. 23) 1946.

ones. Others [45] also found that the antibacterial action of streptomycin differs from that of penicillin. In contrast with penicillin, streptomycin inhibits the growth of bacteria less well in good mediums than in poor. Tubercle bacilli may develop resistance of more than a thousandfold when exposed to streptomycin.[46]

Streptomycin failed to inhibit the multiplication of influenza virus in chick embryos.[47] It is less active than penicillin against experimental syphilis.[48]

New Antibiotic Substances.—Search for other antibiotic substances has led to some unexpected sources. One has been found in Bacillus larvae [49] from honey bee larvae and another in cedar wood.[50] Both agents inhibit the growth of a wide range of both gram-positive and gram-negative bacteria and of fungi. Bacitracin derived from Bacillus subtilis, also inhibitive of pathogenic bacteria, has already been used with success clinically.[51] It may be similar to or identical with the substance studied by Metchnikoff in 1897 and reported on by Ramon as subtiline.[52] Mycocidin is another product of a mold bactericidal for Mycobacterium tuberculosis.[53] Parachlorophenol is an effective agent against gram-negative bacteria in wound infections,[54] and various phenanthrene-related substances—for example, vitamin D, ergosterol, cholesterol and bile salts—have an antibacterial action.[55]

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45. Wallace, G. I., and others: Studies on the Mode of Action of Streptomycin: I. Effect of Culture Media, Proc. Soc. Exper. Biol. & Med. **60**:127-128 (Oct.) 1945.

46. Youmans, G. P., and others: Increase in Resistance of Tubercle Bacilli to Streptomycin: A Preliminary Report, Proc. Staff Meet., Mayo Clin. **21**:126-127 (March 20) 1946.

47. Florman, A. L.; Weiss, A. B., and Council, F. E.: Effect of Large Doses of Streptomycin and Influenza Viruses on Chick Embryos, Proc. Soc. Exper. Biol. & Med. **61**:16-18 (Jan.) 1946.

48. Dunham, W. B., and Rake, G.: The Activity of Streptomycin in Experimental Syphilis, Science **103**:365 (March 22) 1946.

49. Holst, E. C.: An Antibiotic from a Bee Pathogen, Science **102**:593-594 (Dec. 7) 1945.

50. Southham, C. M.: Antibiotic Activity of Extract of Western Red Cedar Heartwood, Proc. Soc. Exper. Biol. & Med. **61**:391-396 (April) 1946.

51. Johnson, B. A.; Anker, H., and Meleney, F. L.: Bacitracin: A New Antibiotic Produced by a Member of the B. Subtilis Group, Science **102**:376-377 (Oct. 12) 1945.

52. A New Antibacterial Substance: Subtiline, Foreign Letters, J. A. M. A. **129**:1281 (Dec. 29) 1945.

53. Gerber, I. E., and Gross, M.: Inhibition of Growth of Mycobacterium Tuberculosis by a Mold Product: The Effect on Pathogenic Human Tubercle Bacilli, Science **103**:167-169 (Feb. 8) 1946.

54. Meleney, F. L., and others: Treatment of Mixed Infections with Penicillin, J. A. M. A. **130**:121-124 (Jan. 19) 1946.

(Footnotes continued on next page)

INFECTIONS OF THE RESPIRATORY TRACT

Increased interest in the minor infections of the respiratory tract, stimulated no doubt by the modern control and subsequent reduction of the incidence of severe bacterial pneumonias, has led to considerable clarification of the problem. A tentative classification of this group of mild diseases may be made on epidemiologic, clinical and etiologic grounds as follows: (*a*) the common cold; (*b*) nonbacterial pharyngitis; (*c*) grip; (*d*) viroid, which includes both mild and pneumonic forms caused by the agents of viral pneumonia, and (*e*) influenza A and B.[56] Abernethy[57] reported that diseases resembling the common cold and exudative (nonbacterial) pharyngitis had been transferred separately to volunteers, indicating an etiologic distinction between the two which had long been suspected. It is still uncertain whether grip is a distinct disease or a group of separate unclassifiable entities which will eventually be included under the other headings. At any rate, further progress of knowledge of the infections may be anticipated. The problem is about to be investigated on a large scale at the National Institute of Health and the Western Reserve University School of Medicine in this country and by the Medical Research Council in England.

According to extensive studies[58] on large groups of soldiers, the ordinary variety of acute infections of the respiratory tract had epidemiologic features distinct from and independent of those of influenza, infections with hemolytic streptococci and rubella, suggesting that they represent either a single entity or a group of similar ones. As was noted in many earlier observations, new recruits are particularly susceptible, and the rapid disappearance of attacks among them suggests the development of immunity. Studies, however, do not support the general impression that the following are the chief factors in the high rate of infection among recruits: (1) exchange of nasopharyngeal flora, (2) exhaustion from unaccustomed duties, (3) reaction to immunization processes, (4) difficulties in psychologic adjustment, (5) unsanitary mess halls or (6) inclement weather. While these may be contributing factors, there is no doubt but that the season of the year is of more

55. Raab, W.: Antibacterial Action of Phenanthrene-Related Substances, Science **103**:670-671 (May 31) 1946.

56. Reimann, H. A.: Viral Infections of the Respiratory Tract, J. A. M. A. **132**:487-493 (Nov. 2) 1946.

57. Abernethy, T. J.: Experimental Transmission of Minor Respiratory Illness to Human Volunteers, read at the meeting of the American Society of Clinical Investigation, 1946.

58. Acute Respiratory Disease Among New Recruits, Commission on Acute Respiratory Disease, Am. J. Pub. Health **36**:439-450 (May) 1946.

importance since, for reasons unknown, epidemics occurred most regularly in the winter and the early spring. Other diseases of the respiratory tract so mild as often to escape detection occur during the summer and the fall.

In the studies of Rantz and associates [59] infections of the respiratory tract due to undetermined viruses did not favor the spread of hemolytic streptococci. Like others, they found that the stress of introducing troops to a new area led to an increase of infections due to viruses and to hemolytic streptococci regardless of duration of military service.

Gamma globulin injected in 4 to 10 cc. amounts had no effect in preventing attacks of an influenza-like infection of the respiratory tract.[60]

Viral Pneumonias.—The most important contribution in this field is a virus recovered from patients which can be maintained by passage in chick embryos, causes pulmonary lesions in hamsters and cotton rats, is neutralized by convalescent serum and can be differentiated from the psittacosis group of organisms by neutralization tests.[61] Eaton [62] estimates that the newly discovered virus is the cause of 60 per cent of the incidence of viral pneumonia; less than 20 per cent is caused by the viruses of influenza and the psittacosis group, a small percentage by the viruses of lymphocytic choriomeningitis and Q fever and the rest by causes yet unknown. If 70 to 80 per cent of the incidence of these forms of pneumonia is caused by viruses, there is no further need to use the undesirable term "atypical pneumonia."

The next point to prove is that some of these forms of pneumonia, except for the psittacosis group, are only the severe forms with pulmonary involvement of a widespread mild infection of the respiratory tract as suggested by Reimann in 1938.[63] In Minnesota an epidemic of an

59. Rantz, L. A., and others: Streptococcic and Nonstreptococcic Disease of the Respiratory Tract: Epidemiologic Observation, Arch. Int. Med. **77**:121-131 (Feb.) 1946.

60. Yannet, H., and Deutsch, J. V.: Gamma Globulin Not Effective in Prophylaxis of Epidemic Respiratory Infections, J. A. M. A. **131**:593 (June 15) 1946.

61. Eaton, M. D.; Meiklejohn, G.; van Herick, W., and Corey, M.: Studies on the Etiology of Primary Atypical Pneumonia: II. Properties of the Virus Isolated and Propagated in Chick Embryos, J. Exper. Med. **82**:317-328 (Nov.) 1945. Eaton, M. D.; van Herick, W., and Meiklejohn, G.: Studies on the Etiology of Atypical Pneumonia: III. Specific Neutralization of the Virus by Human Serum, ibid. **82**:329-342 (Nov.) 1945. Eaton, M. D.: Serological Differentiation of Primary Atypical Pneumonia from Virus Pneumonia of the Psittacosis Group, Proc. Soc. Exper. Biol. & Med. **60**:231-235 (Nov.) 1945.

62. Eaton, M. D.: Recent Observations on Virus Pneumonia, California & West. Med. **63**:113-116 (Sept.) 1945.

63. Reimann, H. A.: An Acute Infection of the Respiratory Tract with Atypical Pneumonia: A Disease Entity Probably Caused by a Filtrable Virus, J. A. M. A. **111**:2377-2384 (Dec. 24) 1938. Reimann, H. A., and Havens, W. P.: An Epidemic Disease of the Respiratory Tract, Arch. Int. Med. **65**:138-150 (Jan.) 1945.

infection of the respiratory tract affected 191 persons over a two month period; of the 191 attacks, 113 were classified as mild, 47 as moderately severe and 31 as severe, some of these with pneumonia.[64] Serum from patients with severe attacks and from some with mild ones showed an increase of antibodies which neutralized Eaton's virus, suggesting that they were of the same origin.

Horsfall and Curnen[65] report the presence of antibodies which neutralize the pneumonitis virus of mice (PVM virus) in rabbits, monkeys, human beings, hamsters, guinea pigs and mice in that order of frequency. The results indicate that PVM virus is widely distributed, even in man. Antibodies to the virus may be stimulated by nonspecific, innocuous measures. Horsfall therefore feels that if specific antibodies develop in animals inoculated with material from patients with viral pneumonia, this means only that their production has been stimulated nonspecifically and does not indicate the passage of the virus. It could be interpreted differently. As mentioned in last year's review, if man, as is now shown, may have had PVM infection, why cannot the virus, which may actually be present, be transmitted to mice? Andrewes[66] discovered in mice a new virus which causes "grey lungs." Adams[67] reports a third epidemic of viral pneumonia among infants in Minnesota. It is remarkable that no report of a similar epidemic occurring elsewhere has been made.

Psittacosis–Ornithosis–S-F Group.—Several more agents of this obviously large and ever widening group of infections have been discovered. Two new ones have been added to the list. One in Chicago, called the Illinois virus,[68] was obtained from 2 patients who died. It was related to, but different from, known viruses of this group. The other one, a virus isolated during an outbreak of a severe form of pneumonia in Louisiana, is apparently also different.[69] A third agent was found to exist normally in the respiratory tracts of mice; it was more like psittacosis virus than Nigg's mouse pneumonitis virus.[70] It is even suggested that the agent of heartwater fever of sheep belongs

64. Breslow, L.: Epidemic of Acute Respiratory Disease Associated with Atypical Pneumonia, J. Clin. Investigation **24**:775-779 (Nov.) 1945.

65. Horsfall, F. L., Jr., and Curnen, E. C.: Studies on Pneumonia Virus of Mice (PVM), J. Exper. Med. **83**:43-64 (Jan.) 1946.

66. Andrewes, C. H., and Glover, R. E.: Grey Lung Virus: An Agent Pathogenic for Mice and Other Rodents, Brit. J. Exper. Path. **26**:379-386, 1945.

67. Adams, J. M.: Third Epidemic of Primary Virus Pneumonia Among Infants in Minnesota, Journal-Lancet **65**:192-193 (May) 1945.

68. Zichis, J., and Shaughnessy, H. J.: Isolation of an Apparently New Virus from Two Fatal Pneumonia Cases, Science **102**:301-302 (Sept. 21) 1945.

69. Larson, C. L., and Olson, B. J.: An Epidemic of Some Pneumonitis in the Bayou Region of Louisiana, Pub. Health Rep. **61**:69-78 (Jan. 18) 1946.

in the group; it is now included with the Rickettsias (R. ruminantium) but may be more closely related to the psittacosis group.[71] Thus far, the following filtrable but visible agents may be tentatively gathered as a group of related pathogens from human and other sources:

Psittacosis virus (birds and man)	Nigg's mouse pneumonitis virus
S-F virus (man)	Louisiana pneumonitis virus (man?)
Ornithosis virus (birds)	Illinois virus (man)
Ailourosis virus (cats)	Fulmar disease virus (birds, man)
Australian mouse virus	Virus of lymphogranuloma venereum (man)
Meningopneumonitis virus (ferrets, man)	Agent of sheep, heartwater fever

Others, no doubt, remain to be discovered. The pneumonia of Q fever, caused by a filtrable rickettsia, is discussed later.

Adams and associates[72] describe an epidemic of 350 cases of viral pneumonia which occurred in Naples in 1945, of which 50 were carefully studied. Unusual features in the outbreak were the failure of cold agglutinin to develop in any instance, a positive heterophilic antibody test in 18 cases, in 10 of which splenomegaly, palpable lymph nodes and macules were noted, and a positive cephalin-cholesterol flocculation test in most cases. There were no increases in the number of lymphocytes or the number of monocytes to suggest infectious mononucleosis. Some of the patients had had malaria. The variations from the usual viral pneumonias suggest that a different causative agent may have been operative. Explosive outbreaks of pneumonia caused by the rickettsia of Q fever also occurred among troops in Italy and in Greece, as discussed under "Rickettsial Diseases."

One author[73] thinks that rheumatic pneumonia may at times be confused with viral pneumonia. Pathologically, the pulmonary reactions are similar. His patient supposedly had viral pneumonia, but nine months later cardiovalvular disease developed. The pneumonia, he thinks, may have been rheumatic pneumonia.

Numerous other clinical reports on the common forms of viral pneumonia were published during the year without much new data

70. DeBurgh, P.; Jackson, A. V., and Williams, J.: Spontaneous Infection of Laboratory Mice with a Psittacosis-Like Organism, Australian J. Exper. Biol. & Med. **23**:106-108 (June) 1945.

71. Rake, G.; Alexander, R., and Hamre, D. M.: The Relationship of the Agent of Heart-Water Fever: Rickettsia Ruminantium, Science **102**:424-425 (Oct. 26) 1945.

72. Adams, A. B., and others: Primary Atypical Pneumonia, Brit. M. J. **1**:227-231 (Feb. 16) 1946.

73. Jensen, C. R.: Non-Suppurative Post-Streptococcic (Rheumatic) Pneumonitis: Pathologic Anatomy and Clinical Differentiation from Primary Atypical Pneumonia, Arch. Int. Med. **77**:237-253 (March) 1946.

being added. In one contribution [74] ulceration of the bronchial tree was described as a complication, but, according to prevailing opinion, complications are rare. Penicillin is of no value in the treatment of viral pneumonia.[75]

Cold agglutination of erythrocytes was discussed in several papers.[76] The consensus is that cold agglutinin in a titer of 1 : 40 or more develops late in the majority of cases of viral pneumonia not of the psittacosis group, that it appears in persons who have not been sick recently, probably as a result of symptomless infection, and it often occurs in a titer lower than 1 : 40 after many other infections.[77]

Influenza.—It is generally agreed that vaccination against influenza A and influenza B confers a degree of immunity, lasting for a variable time. Most studies indicate that there are fewer attacks in those who have been vaccinated than in those who have not. Because of the promising results, more than 5,000,000 doses of vaccine were given to soldiers in 1943-1944 and even more in 1945-1946.[78] This project is one of the most extensive medical experiments ever performed. The results are not as yet reported. According to Francis and co-workers,[79] the incidence of influenza B among 600 vaccinated men was 1.15 per cent, compared with 9.9 per cent in 1,100 unvaccinated ones. There is evidence that the immunity may last for a year after vaccination and that refrigerated vaccine is stable for more than a year.[80] Antibodies were demonstrable in 69 per cent of vaccinated persons for four months and in 66 per cent for a year.

According to Francis and co-workers,[79] there was continued but shifting prevalence of influenza B over eight months in 1945 before an outbreak large enough to attract attention occurred. Influenza B was

74. Kay, E. B.: Ulcerative Tracheobronchitis Following Atypical Pneumonia, Arch. Int. Med. **76**:93-101 (Aug.) 1945.

75. Allison, S. T.: Penicillin in Primary Atypical Pneumonia with Report of Twenty-eight Cases, U. S. Nav. M. Bull. **45**:930-932 (Nov.) 1945.

76. Springarn, C. L., and Jones, J. P.: Cold Hemagglutination in Primary Atypical Pneumonia and Other Common Infections, Arch. Int. Med. **76**:75-87 (Aug.) 1945.

77. Finland, M.; Peterson, O. L.; Allen, H. E.; Samper, B. A.; Barnes, M. W., and Stone, M. B.: Cold Agglutinins: I. Occurrence of Cold Isohemagglutinin in Various Conditions, J. Clin. Investigation **24**:451-457 (July) 1945.

78. New Influenza Vaccine Going to Civilians Next Year, Washington Letter, J. A. M. A. **130**:40 (Jan. 5) 1946.

79. Francis, T.; Salk, J. E., and Brace, W. M.: The Protective Effect of Vaccination Against Epidemic Influenza B, J. A. M. A. **131**:275-278 (May 25) 1945. Salk, J. E., and Francis, J.: Immunization Against Influenza, Ann. Int. Med. **25**: 443-452 (Sept.) 1946.

80. Salk, J. E.; Pearson, H. E.; Brown, P. N.; Smyth, C. J., and Francis, T.: Immunization Against Influenza with Observations During an Epidemic of Influenza A One Year After Vaccination, Am. J. Hyg. **42**:307-322 (Nov.) 1945.

prevalent for a year in the form of a smoldering epidemic, which without etiologic proof of its identity could have been mistaken for a series of unrelated episodes here and there. The disease was usually mild, but severe forms, with pneumonia, were recognized. Isolated attacks which ordinarily would have been considered to be undifferentiated mild respiratory infections were demonstrated to be influenza B by serologic tests. Similar observations and studies were made by Sigel and co-workers [81] and by Burnet and co-workers [82] in Australia.

In an explosive outbreak of influenza A in San Antonio, Texas, 28 per cent of 39 patients had roentgenographic evidence of pulmonary involvement.[83] The occurrence of viral pneumonia of other origin, nasopharyngitis and pneumococcic pneumonia was uninfluenced by the epidemic. Over a period the relative distribution of cases of the various diseases was: influenza, 25 per cent; lobar pneumonia, 34 per cent; nasopharyngitis, 45 per cent, and viral pneumonia, 13 per cent.

Different strains of influenza A virus when inoculated in human subjects caused disease of different degrees of severity with different periods of incubation.[84] Epidemics of influenza may be caused by influenza A virus in two to three year cycles and by influenza B virus in four to six year cycles. The dominant factor controlling the occurrence of epidemics seems to be the balance between immune and susceptible persons in the population.[85]

Further evidence of the occurrence of bacterial pneumonias as secondary manifestations of influenza is given in a report of influenza B and type I pneumococcic pneumonia concurrent in a community.[86]

Burnet [87] adds further support to his view of the different culture phases of influenza viruses. The virus which resides in the body to cause influenza is in the so-called O phase, and as soon as it is trans-

81. Sigel, M. M.; Hart, M. M.; Hobbs, G., and Guthner, B.: Demonstration of Influenza Virus, Type B, in a Recent Outbreak of Upper Respiratory Infection, Science **102**:646 (Dec. 21) 1945.

82. Burnet, F. M.; Stone, J. D., and Anderson, S. G.: An Epidemic of Influenza B in Australia, Lancet **1**:807-811 (June 1) 1946.

83. Pollard, M.; Kalkstein, M., and Livesay, H. R.: The Influenza Epidemic of 1943-1944 in San Antonio, Texas, Am. J. Trop. Med. **26**:141-143 (Jan.) 1946.

84. Henle, W.; Henle, G.; Stokes, J., and Maris, E. P.: Experimental Exposure of Human Subjects to Viruses of Influenza, J. Immunol. **52**:145-166 (Feb.) 1946.

85. The Periodicity of Influenza, The Commission on Acute Respiratory Diseases, Am. J. Hyg. **43**:29-37 (Jan.) 1946.

86. The Relation Between Epidemics of Acute Bacterial Pneumonia and Influenza, Commission on Acute Respiratory Diseases, and the New York State Department of Health, Science **102**:561-563 (Nov. 30) 1945.

87. Burnet, F. M., and Stone, J. D.: The Significance of Primary Isolation of Influenza Virus by Inoculation of Mice or of the Allantoic Cavity of Chick Embryos, Australian J. Exper. Biol. & Med. **23**:147-150 (June) 1945.

ferred to animal hosts, it transforms into the D phase. Virus in the O phase cannot invade mice until it changes into the D phase.

Adams and associates [88] examined smears from the pharynxes of patients with influenza A. Characteristically there were large sheets of sloughed-off epithelial cells and an exudate composed mainly of mononuclear cells. The latter is characteristic of other viral infections as well, but the procedure may be used to differentiate viral infections of the pharynx from bacterial or fungous infections, in which the exudate is predominantly of polymorphonuclear cells.

Sulfonamide Compounds Used for Prophylaxis.—The enthusiasm incident to the reports that sulfonamide compounds had been used to prevent infections of the respiratory tract in numerous military groups in the past few years must be tempered by the fulfilment of certain predicted consequences. Sulfadiazine suppressed infections with hemolytic streptococci for a time among naval personnel, but during the experiment hemolytic streptococci of types 17 and 19 were sulfonamide resistant, or became so, and gave rise to a serious epidemic.[89] Sulfadiazine prophylaxis even seemed to increase susceptibility to infection, especially to scarlet fever. A similar experience is reported by Damrosch.[90] Sulfadiazine gave no worth while benefit in an outbreak of sore throat caused by type 5 hemolytic streptococci from food poisoning.[91]

Other studies [92] showed that sulfadiazine and sulfathiazole not only failed to shorten severe attacks of sore throat due to hemolytic streptococci, but seemed to harm the patient; treated patients did not feel as well on the tenth day as many untreated ones did on the fifth. Spink's group [25] reports similar results.

In a further report of studies [93] on the prevention of air-borne infections, the oiling of bedding and of floors with Triton oil emulsion (T-13) was successful in reducing the amount of dust and pathogenic

88. Adams, J. M.; Pennoyer, M. M., and Whiting, A. M.: Pathologic Study of the Acutely Inflamed Human Pharynx in Influenza A Infections, Am. J. Dis. Child. **71**:162-170 (Feb.) 1946.

89. Sulfadiazine Resistant Strains of Beta Hemolytic Streptococci, Epidemiologic Unit no. 22, J. A. M. A. **129**:921-927 (Dec. 1) 1945.

90. Damrosch, D. S.: Chemoprophylaxis and Sulfonamide Resistant Streptococci, J. A. M. A. **130**:124-128 (Jan. 19) 1946.

91. A Study of Foodborne Epidemic of Tonsillitis and Pharyngitis Due to B. Hemolytic Streptococcus, Type 5, Commission on Acute Respiratory Diseases, Bull. Johns Hopkins Hosp. **77**:143-210 (Sept.) 1945.

92. Clodfelter, H. M.: Treatment of Severe Acute Tonsillitis With and Without Sulfonamides, Ohio State M. J. **41**:819-820 (Sept.) 1945.

93. Loosli, C. G., and others: Oil Treatment of Bedclothes for the Control of Dust-Borne Infection: II. Use of Triton Oil Emulsion (T-13) as a Routine Laundry Procedure, Am. J. Hyg. **43**:105-115 (March) 1946.

agents in the air of barracks. The measure promises to be of aid in the reduction of air-borne infections in crowded rooms.

Prevention of Pneumococcic Pneumonia.—In a well controlled study, MacLeod and his group [94] were able to demonstrate the effectiveness of polysaccharides of pneumococci used as specific vaccines against pneumococcic pneumonia. Solutions containing the capsular substances of pneumococci of types I, II, V and VII were used to immunize a population in which pneumonias of these types and also of types XII and IV had been prevalent. Pneumonias caused by pneumococci of the same types which were used for immunization were greatly reduced, while the numbers of infections with types XII and IV were about the same as in preceding years. There was a reduction of pneumonias of types I, II, V and VII even among nonvaccinated persons, suggesting that the reduction of attacks among those who were vaccinated reduced the carrier rate and lessened the general dispersion of these types, with subsequent reduction of contagion.

Phagocytosis of a pneumococcus depends not only on the presence of specific antibody or an injury of the capsule of the pneumococcus but also on certain nonspecific surface phenomena which aid in recovery from infection.[95]

Another case of pneumonia was diagnosed as due to Streptococcus viridans infection because this bacterium was found in smears and cultures of the sputum in "pure" growth.[96] The number of leukocytes was normal, and the disease described seemed to represent viral pneumonia, with which the author says streptococcic pneumonia is usually confused. It is doubtful if Str. viridans ever causes pneumonia or that penicillin cured the disease in question. The author does not report any attempt to compare the streptococcus recovered with streptococcus MG or 344, believed by some investigators to be associated with viral pneumonias. The author also perpetuates a curious descriptive error in stating that "prune juice" sputum occurs in pneumonia. Sputum resembling the thin brown juice of prunes rarely if ever occurs in pneumonia.

Another doubtful case was reported, in which the patient was a 7 month old infant.[97]

94. MacLeod, C. M., and others: Prevention of Pneumococcal Pneumonia by Immunization with Specific Capsular Polysaccharides, J. Exper. Med. **82**:445-465 (Dec.) 1945.

95. Wood, W. B.; Smith, M. R., and Watson, B.: Surface Phagocytosis: Its Relation to the Mechanism of Recovery in Pneumococcal Pneumonia, Science **104**: 28-29 (July 12) 1946.

96. Solomon, S.: Case of Streptococcus Viridans Pneumonia Successfully Treated with Penicillin, Am. J. M. Sc. **210**:431-435 (Oct.) 1945.

97. Reinhart, J. B., and Venning, W. L.: Pneumonia Due to Streptococcus Viridans, J. Pediat. **27**:480-483 (Nov.) 1945.

DISEASES CAUSED BY VIRUSES

Poliomyelitis.—After years of study and controversy, the epidemiology of poliomyelitis seems to be greatly clarified. It has been uncertain whether the virus leaves the patient or the carrier chiefly by way of the feces, the oropharyngeal secretions or the blood; whether the infection is water borne, food borne or air borne or is transmitted by insects or by direct contact and whether the route of entry is the gastrointestinal tract, the respiratory tract or insect punctures of the skin. Each view has its proponents, and it is probable that most of them are partly correct. It is probable that various factors play a role. The problem is to determine which ones are the most important. Several studies cast light on the matter.

Casey's group [98] made a survey of poliomyelitis in Chicago in a nonepidemic year. The disease was apparently highly contagious among children less than 3½ years old, in whom the morbidity rate was 90 per cent. Multiple occurrences of the disease in a family were the rule, but since less than 1 of 6 patients became paralyzed, the majority of attacks were not recognized as those of poliomyelitis unless special diagnostic tests were made. Patient to patient contact seemed to be the most important mode of transmission. There was no evidence that flies played a major role, once the epidemic began.

Observations along similar lines were made in Buffalo on an epidemic which at first thought would have been regarded as an "original" or an isolated outbreak. Attention was directed to the outbreak by the development of paralysis in a patient who in the absence of further information may have been wrongly considered as the source of infection. A study by Smith's group [99] showed that other patients with undiagnosed mild attacks were present in the community at the same time and had been for some time before. Poliomyelitis had occurred in the community apparently sporadically for at least five months, and the virus had survived and passed unrecognized through a chain of patients with nonparalytic attacks until one with paralysis attracted attention during a small epidemic. Person to person contact was thought to account for the perpetuation of the disease.

Brown and co-workers [100] studied an outbreak in a summer camp. The virus was found in the feces of 5 of 6 cabin mates of a patient in

98. Casey, A. E.; Fishbein, W. I., and Bundesen, H. N.: Transmission of Poliomyelitis by Patient to Patient Contact, J. A. M. A. **129**:1141-1145 (Dec. 22) 1945.

99. Smith, M. L.; Bridge, E. M.; Underwood, H. E., and Dale, G. E.: A Study of the Origin of an Epidemic of Poliomyelitis, J. A. M. A. **127**:1150-1156 (Dec. 22) 1945.

100. Brown, G. C.; Francis T., and Pearson, H. E.: Rapid Development of Carrier State and Detection of Poliomyelitis Virus, J. A. M. A. **129**:121-123 (Sept. 8) 1945.

whom poliomyelitis developed during a period of six days of contact. In one of the carriers poliomyelitis developed nineteen days after his feces were found to harbor the virus. The virus was present in the patient's pharynx during the disease. It may be recalled from previous studies that the virus was recovered from the oropharynx early in the disease in 50 per cent of the cases. The presence of the virus in the stool, however, does not constitute evidence that it entered through the respiratory tract or the gastrointestinal tract, since Melnick [101] caused the virus to appear in the stools of monkeys inoculated parenterally. The virus may appear in the stools for two to four weeks before symptoms develop. In a series of papers published by Melnick's group [102] it is shown that poliomyelitis virus, usually believed to disappear rather rapidly from the stools during convalescence, was still present in 13 per cent of 61 patients in the eighth week. In no case was the state of carrier prolonged as in cases of typhoid. Virus was detected for the first time in the blood of the patient. In another study the virus was isolated from the water of a creek near the residence of several patients.[103] That other modes of transmission are also of importance was illustrated in an explosive outbreak of poliomyelitis in a naval training school.[104] Eighteen attacks were diagnosed, and at least 100 milder ones developed within an eight day period. Evidence pointed to milk, possibly contaminated by flies, as the source of the infection.

These observations favor the view that poliomyelitis is transmitted chiefly in person to person contact by respiratory and oral transfer. Although murine strains of poliomyelitis virus were isolated from mice

101. Melnick, J. L.: The Recovery of Poliomyelitis Virus from the Stools of Monkeys and Chimpanzees Experimentally Infected by Various Routes, Federation Proc. **5**:250-251 (Feb.) 1946.

102. Horstmann, D. M.; Melnick, J. L., and Wenner, H. A.: Isolation of Poliomyelitis Virus from Human Extraneural Sources: Comparison of Virus Content of Pharyngeal Swabs, Oropharyngeal Washings and Stools of Patients, J. Clin. Investigation **25**:270-274 (March) 1946. Melnick, J. L.; Horstmann, D. M., and Ward, R.: Isolation of Poliomyelitis Virus from Human Extraneural Sources: Comparison of Virus Content of Blood, Oropharyngeal Washings and Stools of Contacts, ibid. **25**:275-277 (March) 1946. Horstmann, D. M.; Ward, R., and Melnick, J. L.: Isolation of Poliomyelitis Virus from Human Extraneural Sources: Persistence of Virus in Stools After Acute Infection, ibid. **25**:278-283 (March) 1946. Ward, R.; Horstmann, D. M., and Melnick, J. L.: Isolation of Poliomyelitis Virus from Human Extraneural Sources: Search for Virus in Blood of Patients, ibid. **25**:284-286 (March) 1946.

103. Toomey, J. A.; Takacs, W. S., and Weaver, H. M.: Isolation of Poliomyelitis Virus from Creek Water by Direct Transmission to Cotton Rat, Am. J. Dis. Child. **70**:293-297 (Nov.-Dec.) 1945.

104. Goldstein, D. M.; Hammon, W. M., and Viets, H. R.: An Outbreak of Polioencephalitis Among Navy Cadets, Possibly Food Borne, J. A. M. A. **131**:569-573 (June 15) 1946.

in New York, Jungeblut and Dalldorf [105] do not consider virus-harboring mice as a source of poliomyelitis in man.

Jungeblut's suggestion that a number of apparently similar viruses be included in a "poliomyelitis group" has not been generally adopted. There is reason to believe that several similar viruses may be included in a "poliomyelitis group." Further support for this view accrues in a study in which immunologic relations to other strains were found in one poliomyelitis virus which in its virulence for hamsters differed from the usual classic viruses, the Lansing strain and Theiler's mouse encephalomyelitis virus.[106]

That tonsillectomy and the development of the bulbar form of poliomyelitis are related is reemphasized by studies of an epidemic in which it was found that 43 per cent of the children with this form of the disease had undergone tonsillectomy in the previous thirty days.[107] The incidence of poliomyelitis in children who had recently had their tonsils removed was 2.6 times that in other children, and that of the bulbar form was 16 times greater. According to Bodian,[108] lesions of the brain alone can produce the spasticity of acute poliomyelitis, and neither activity of the virus nor lesions of the spinal cord need be present. Nelson [109] suggests that a disturbance of the circulation and edema of the spinal cord are factors in the cause of the paralysis.

Aside from subjective improvement in a few of 34 patients with poliomyelitis, no encouraging results came from treatment with curare. According to Fox,[110] curare is too dangerous a drug to be used in the acute phase of the disease. There is no evidence that gamma globulin or that serum in any form is of value in the treatment of the disease.[111]

In a study to determine whether deficiency of other vitamins besides thiamine results in increased resistance of mice to poliomyelitis virus, it was observed that deficiency of pyridoxine, inositol and biotin caused

105. Jungeblut, C. W., and Dalldorf, G.: Epidemiological and Experimental Observations of Poliomyelitis in New York City (1943-1944), Am. J. Hyg. **46**:49-64 (Jan.) 1946.

106. Dalldorf, B., and Whitney, E.: Immunologic Relationships of MM, Lansing Poliomyelitis and Mouse Encephalomyelitis Virus, Proc. Soc. Exper. Biol. & Med. **59**:150-155 (June) 1945.

107. Anderson, J. A.: Poliomyelitis and Recent Tonsillectomy, J. Pediat. **27**: 68-70 (July) 1945.

108. Bodian, D.: Experimental Evidence on the Cerebral Origin of Muscle Spasticity in Acute Poliomyelitis, Proc. Soc. Exper. Biol. & Med. **61**:170-175 (Feb.) 1946.

109. Nelson, N.: Spinal Cord Circulation in Poliomyelitis, Science **104**: 49-50 (July 19) 1946.

110. Fox, M. J.: Curare in the Treatment of Acute Poliomyelitis, J. A. M. A. **131**:278-280 (May 25) 1946.

111. Bahlke, A. M., and Perkins, J. E.: Treatment of Preparalytic Poliomyelitis with Gamma Globulin, J. A. M. A. **129**:1146-1150 (Dec. 22) 1945.

no striking changes in the mice as compared with the controls.[112] Thiamine deficiency seems to be a specific factor in mice.

Mice treated with thiouracil are more susceptible to the virus of poliomyelitis than normal ones, but mice given thyroid substance are less so.[113]

St. Louis Encephalitis.—During interepidemic years 12 cases of St. Louis encephalitis, among 66 cases of acute encephalitis, were studied in a St. Louis hospital.[114] Like the epidemic cases, all the sporadic cases occurred in the summer. It is obvious that the disease is endemic, probably maintained in a reservoir of blood-sucking ticks, mites or mosquitoes.

Virusemia was demonstrated for the first time.[115]

Lymphocytic Choriomeningitis.—Mice may serve as a source of lymphocytic choriomeningitis. This disease occurred in 3 members of a household where infected mice were trapped.[116] About 4 per cent of mice infesting houses in New York city carry the virus.

Japanese Encephalitis (Epidemic Encephalitis Type B).—Encephalitis caused by type B virus occurred in natives in the RyuKyu Islands in July 1945.[117] One American soldier contracted the disease. This observation raises the question whether carriers have developed in troops of the United States and whether the infection will be brought to this country by returning veterans. At least seven species of mosquitoes in North America are capable of carrying the virus.[118] Horses may be epidemiologic factors in Okinawa.[119]

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112. Lichstein, H. C., and others: Influence of Pyridoxine, Inositol and Biotin on Susceptibility of Swiss Mice to Experimental Poliomyelitis, Proc. Soc. Exper. Biol. & Med. **60**:279-284 (Nov.) 1945.

113. Holtman, D. F.: The Effect of Thiouracil and Thyroactive Substances on Mouse Susceptibility to Poliomyelitis Virus, Science **104**:50-51 (July 19) 1946.

114. Blattner, R. J., and Heys, F. M.: St. Louis Encephalitis, J. A. M. A. **130**:854-857 (Nov. 24) 1945.

115. Blattner, R. J., and Heys, F. M.: Isolation of St. Louis Encephalitis from the Peripheral Blood of a Human Subject, J. Pediat. **28**:401-406 (April) 1946.

116. Dalldorf, G.; Jungeblut, C. W., and Umphlet, M. D.: Multiple Cases of Choriomeningitis in an Apartment Harboring Infected Mice, J. A. M. A. **131**:25 (May 4) 1946.

117. Hodes, H. L.; Thomas, L., and Peck, J. L.: Cause of an Outbreak of Encephalitis Established by Means of Complement-Fixation Tests, Proc. Soc. Exper. Biol. & Med. **60**:220-225 (Nov.) 1945.

118. Reeves, W. C., and Hammon, W. M.: Laboratory Transmissions of Japanese B Encephalitis Virus by Seven Species (Three Genera) of North American Mosquitoes, J. Exper. Med. **83**:185-194 (March) 1946.

119. Thomas, L., and Peck, J. L.: Results of Inoculating Okinawian Horses with the Virus of Japanese B Encephalitis, Proc. Soc. Exper. Biol. & Med. **61**:5-6 (Jan.) 1946.

Russian or Far Eastern tick-borne, spring-summer encephalitis is reviewed in a special supplement of the *American Review of Soviet Medicine*, 1946.

A hitherto undescribed form of viral encephalomyelitis was reported as occurring in water buffaloes of the western part of China.[120] The infection was transmitted to goats, guinea pigs and rabbits. It may have occurred in man through contact, but no case of this has as yet been recognized.

Smithburn and his associates [121] report another "new" neurotropic virus isolated from mosquitoes in Africa, which they named Bunyamwera virus. Specific neutralizing antibodies were demonstrated in a number of persons in the area, which suggests that they had been infected previously.

Mumps.—Clinical and subclinical meningoencephalitis developed in 43 of 100 patients with mumps.[122] Its occurrence was unrelated to the severity of salivary gland or orchitic involvement. A diagnosis can be made in the absence of the usual manifestations of the disease by specific serologic tests. Gamma globulin from mumps convalescent serum, but not that from pooled normal serums, seems to have some effect in the prevention of orchitis when given early in mumps.[123] Rambar's [124] studies show that orchitis developed in 16 per cent of patients who had received 40 cc. of mumps convalescent serum on admission and in 29 per cent of those who had not. Encephalitis occurred regardless of serum treatment. Serum given therapeutically had little or no effect in shortening the disease.

Rubella.—As Albaugh [125] points out, it is strange that no one before Gregg in 1942 was aware of the harmful effect which rubella (German measles) occurring in the mother during pregnancy has on the fetus, but a number of observers have since corroborated the observation. The critical period for the attack seems to be the first two months;

120. Sheng, T. S.: Virus Encephalitis in Buffaloes, Science **103**:344-346 (March 15) 1946.

121. Smithburn, K. C.; Haddow, A. J., and Mahoffy, A. F.: A Neurotropic Virus Isolated from Aedes Mosquitoes Caught in the Semliki Forest, Am. J. Trop. Med. **26**:189-208 (March) 1946.

122. Holden, E. M.; Eagles, A. Y., and Sturns, J. E.: Mumps Involvement of the Central Nervous System, J. A. M. A. **131**:382-385 (June 1) 1946.

123. Gellis, S. S.; McGuinness, A. C., and Peten, M.: A Study on the Prevention of Mumps Orchitis by Gamma Globulin, Am. J. M. Sc. **210**:661-664 (Nov.) 1945.

124. Rambar, A. C.: Mumps: Use of a Convalescent Serum in Treatment and Prophylaxis of Orchitis, Am. J. Dis. Child. **71**:1-13 (Jan.) 1946.

125. Albaugh, C. H.: Congenital Anomalies Following Maternal Rubella in Early Weeks of Pregnancy, J. A. M. A. **129**:719-723 (Nov. 10) 1945.

100 per cent of fetuses of mothers contracting rubella in this period are said to be injured. Of mothers contracting rubella in the third month, 50 per cent give birth to infants with congenital anomalies. The commonest defects are cataracts, cardiac septal defects, patent ductus arteriosus, deafness and microcephaly. Nearly all the infants are poorly developed. The observations indicate the need for enforcing strict preventive measures against rubella in pregnant women and for removing the stigma of hereditary transmission from defects of which rubella is the cause. One wonders whether other severe exanthems may give rise to similar defects in fetuses. Studies in Milwaukee do not bear out the high incidence of the condition. In a large outbreak of rubella [126] 9 women who were in an early stage of pregnancy contracted the disease. One bore a stillborn hydroencephalic infant; the offsprings of the rest were normal. One woman who did not have rubella bore an infant with congenital cataracts.

Infectious Hepatitis.—In a group of 572 campers infectious hepatitis affected 350 persons in a seven week period; [127] 95 of these did not have jaundice. Infection was traced to a well that was probably polluted by cesspool drainage. Feces were thought to be the source of the infection because: in transmission experiments, water from the well caused mild attacks in 4 of 5 volunteers; volunteers inoculated with nasopharyngeal washings and with urine showed no effect; the causative filtrable agent was present in the blood and in the feces. In other experiments it was found that 1 part per million of chlorine added to the water was not enough to inactivate the virus.[128] It was necessary to maintain a concentration of 15 parts per million for thirty minutes. Treatment with sodium carbonate, aluminum sulfate and activated carbon did not completely inactivate the virus. In two other outbreaks circumstantial evidence suggested food as the source of the infection. In one outbreak milk was suspected,[129] and in the other [130] all victims of one epidemic ate meals together. In the latter there was a striking involvement of the lymphatic system resembling infectious mononucleosis, but there were no significant changes in the number or the kind of leukocytes in

126. Fox, M. J., and Bortin, M. M.: Rubella in Pregnancy Causing Malformation in the Newborn, J. A. M. A. **130**:568-569 (March 2) 1946.

127. Neefe, J. R., and Stokes, J.: An Epidemic of Infectious Hepatitis Apparently Due to a Water Borne Agent, J. A. M. A. **128**:1063-1075 (Aug. 11) 1945.

128. Neefe, J. R., and others: Disinfection of Water Containing Causative Agent of Infectious (Epidemic) Hepatitis, J. A. M. A. **128**:1076-1080 (Aug. 11) 1945.

129. Murphy, W. J., and Petrie, L. M.: Outbreak of Infectious Hepatitis, Apparently Milk-Borne, Am. J. Pub. Health **36**:169-173 (Feb.) 1946.

130. Read, M. R., and others: Infectious Hepatitis: Presumably Food-Borne Outbreak, Am. J. Pub. Health **36**:367-370 (April) 1946.

the blood. The epidemiologic features of infectious hepatitis are reviewed by Havens.[131]

The globulin of human immune serum (gamma globulin) is effective in preventing infectious hepatitis if injected intramuscularly during an outbreak.[132] The passive immunity apparently lasts six to eight weeks. The globulin does not influence an attack if injected within six days before the onset or after the disease has begun.

Further experiments were made to learn whether infectious, or epidemic, hepatitis is identical with homologous serum jaundice. Havens [133] demonstrated in volunteers convalescent from serum jaundice a lack of immunity when they were inoculated with a strain of the virus of infectious hepatitis six months later, but this is in contrast with the previous report of Oliphant. The incubation period of infectious hepatitis was the same, twenty to thirty-four days if the inoculum was injected parenterally or fed. Havens' strain of infectious hepatitis virus inoculated parenterally or orally gives an incubation period of fifteen to thirty-four days, in contrast with fifty-six to one hundred and thirty-four days for the virus of homologous serum jaundice. The serum jaundice strain is not infectious if given orally, nor does it appear in the stools as the other virus does. Hepatitis virus injected parenterally does appear in the feces.[134] The inference is that the strains are different. Perhaps, as with other infectious agents, a group of similar and related viruses is operative. Others [135] were unable to transmit serum jaundice to volunteers by feeding stools from patients with serum jaundice but succeeded when stools from patients with infectious hepatitis were used. This may explain why epidemics of jaundice may arise from patients

131. Havens, W. P.: Epidemiological Studies on Infectious Hepatitis, Am. J. Pub. Health **36**:37-44 (Jan.) 1946.

132. Gellis, S. S., and others: The Use of Human Immune Serum Globulin (Gamma Globulin) in Infectious (Epidemic) Hepatitis in the Mediterranean Theater of Operation, J. A. M. A. **128**:1062-1063 (Aug. 11) 1945; The Use of Human Immune Serum Globulin (Gamma Globulin) in Infectious (Epidemic) Hepatitis in the Mediterranean Theater of Operation: II. Studies of Treatment in an Epidemic of Infectious Hepatitis, ibid. **128**:1158-1159 (Aug. 18) 1945. Havens, W. P., and Paul, J. R.: Prevention of Infectious Hepatitis with Gamma Globulin, ibid. **129**:270-272 (Sept. 22) 1945.

133. Havens, W. P.: Experiment in Cross Immunity Between Infectious Hepatitis and Homologous Serum Jaundice, Proc. Soc. Exper. Biol. & Med. **59**: 148-150 (June) 1945.

134. Havens, W. P., Jr.: Elimination in Human Feces of Infectious Hepatitis Virus Parenterally Introduced, Proc. Soc. Exper. Biol. & Med. **61**:210-212 (March) 1946; Viruses of Infectious Hepatitis and Serum Jaundice, Federation Proc. **5**:248 (Feb., pt. 2) 1946.

135. Neefe, J. R.; Stokes, J., and Reinhold, J. G.: Oral Administration to Volunteers of Feces from Patients with Homologous Serum Hepatitis and Infectious (Epidemic) Hepatitis, Am. J. M. Sc. **210**:29-32 (July) 1945.

with infectious hepatitis but not from those with serum jaundice. Three instances of hepatitis transmitted to recipients of transfusions of blood from donors who were in the incipient stage of the disease are reported. In Murphy's 2 patients [136] the period of incubation was twenty-four and forty-seven days, respectively, and in the patient studied by Francis' group,[137] eleven days. To reduce the danger that serum jaundice will be transmitted to persons who receive transfusions or injections of serum, Loutit and Maunsell [138] recommend that when possible the blood be taken from single sources rather than from pooled supplies. Freeman,[139] reverting to the problem of the jaundice that developed in persons vaccinated against yellow fever, suggests that the vaccine itself did not contain the infectious agent but had the property of predisposing its recipients to infectious hepatitis. He bases his views on the spatial and temporal grouping of attacks of jaundice in a military camp. It also seems possible in this instance, however, that an outbreak of post-vaccinal hepatitis coincided with an epidemic of infectious hepatitis.

Evidence of hepatitis or of an injury of the liver persists for many months in a certain proportion of the patients. In one group 18 per cent had prolonged lassitude, mental depression, abdominal discomfort, dyspepsia, subclinical jaundice and low fever.[140]

In the series of patients studied by Hoagland and Shank,[141] prompt hospitalization and rest were of greatest importance in treatment. No effect was noted from methionine, choline or liver extract or from diets high in protein or in carbohydrate when treated patients were compared with a control series. Recrudescences occurred in 18 per cent of patients. Observation has shown that the disappearance of jaundice does not always coincide with recovery.[142] Exercise during active hepatitis causes a measurable increase in the size of the liver, tenderness and

136. Murphy, H. M.: Transmission of Infectious Hepatitis by Blood Transfusion: Report of Two Cases, Gastroenterology **5**:449-456 (Dec.) 1945.

137. Francis, T.; Frisch, A. W., and Quilligan, J. J.: Demonstration of Infectious Hepatitis Virus in Presymptomatic Period After Transfer by Transfusion, Proc. Soc. Exper. Biol. & Med. **61**:276-280 (March) 1946.

138. Loutit, J. F., and Maunsell, K.: Prevention of Homologous Serum Jaundice, Brit. M. J. **2**:759-760 (Dec. 1) 1945.

139. Freeman, G.: Epidemiology and Incubation Period of Jaundice Following Yellow Fever Vaccination, Am. J. Trop. Med. **26**:15-23 (Jan.) 1946.

140. Barker, M. H.; Capps, R. B., and Allen, F. W.: Chronic Hepatitis in the Mediterranian Theater: A New Clinical Syndrome, J. A. M. A. **129**:653-659 (Nov. 3) 1945.

141. Hoagland, C. L., and Shank, R. E.: Infectious Hepatitis: A Review of Two Hundred Cases, J. A. M. A. **130**:615-621 (March 9) 1946.

142. Capps, R. B., and Barker, M. H.: The Significance of Rest and Exercise in the Diagnosis and Management of Infectious Hepatitis, read at the meeting of the American Society of Clinical Investigation, 1946.

evidence of hepatic dysfunction, even without jaundice, an observation which emphasizes the importance of rest in treatment.

In 2 of 23 volunteers with infectious hepatitis, bacteremia with Salmonella cholerae suis developed. This occurrence suggests to Havens and Wenner [143] that infectious hepatitis may render the intestinal tract more susceptible to bacterial invasion. It may also explain the error made many years ago of ascribing the cause of infectious hepatitis to paratyphoid bacilli secondarily present in the blood. The name S. cholerae suis, or "hog cholera bacilli," represents an error of this sort. An example of a similar circumstance with a different disease probably occurred in an outbreak of infantile diarrhea.[144] A bacillus, tentatively called B. mucosus capsulatus, was recovered from the stools of most patients. It may have been a commensal.

Because jaundice at times relieves the symptoms of rheumatoid arthritis, 312 arthritic patients were inoculated with blood from patients with infectious hepatitis;[145] jaundice developed in only 32 of them. Ten were relieved of pain, and a few others were more comfortable, but the effect was short lived. This method of treatment is not recommended, because of the possible dangers of the induced disease.

Viral Myocarditis.—What appears to be a newly discovered filtrable virus able to cause myocarditis in animals was recovered from 2 monkeys by Helwig and Schmidt.[146] The virus was passed through many mice and regularly caused paralysis and myocarditis.

Although filtrable viruses are seldom regarded as the cause of myocardial disease occurring in man, the evidence that myocarditis due to such a virus occurs in monkeys, just described, is strongly suggestive that it may occur in man. That a specific myocardial disease accompanies mumps and influenza has been suspected for many years. Rosenberg [147] now reports evidence of myocardial involvement in 15 per cent of 104 cases of mumps. These reports, together with Finland's recent demonstration of myocarditis in a patient with influenza A, leave little doubt that viruses do cause myocarditis. Electrocardiographic changes

143. Havens, W. P., and Wenner, H. A.: Infectious Hepatitis Complicated by Secondary Invasion with Salmonella, J. Clin. Investigation **25**:45-52 (Jan.) 1946.

144. Walcher, D. N.: "Bacillus Mucosus Capsulatus" in Infantile Diarrhea, J. Clin. Investigation **25**:103-106 (Jan.) 1946.

145. Gardner, F.; Stewart, A., and MacCallum, F. O.: Therapeutic Effect of Induced Jaundice in Rheumatoid Arthritis, Brit. M. J. **2**:677-679 (Nov. 17) 1945.

146. Helwig, F. C., and Schmidt, E. C. H.: A Filter-Passing Agent Producing Interstitial Myocarditis in Anthropoid Apes and Small Animals, Science **102**: 31-33 (July 13) 1945.

147. Rosenberg, D. H.: Acute Myocarditis in Mumps (Epidemic Parotitis), Arch. Int. Med. **76**:257-267 (Nov.-Dec.) 1945.

in 4 cases of infectious mononucleosis suggested pericardial involvement.[148]

DISEASES PROBABLY CAUSED BY VIRUSES

Mononucleosis.—Fifteen patients with infectious mononucleosis gave evidence of hepatic disease but without jaundice.[149] Jaundice is well known to occur in patients with this disease and is usually ascribed to mechanical obstruction of the bile ducts by swollen lymph nodes. Evidence in mononucleosis now indicates the occurrence of active hepatitis akin to infectious hepatitis. Chronic hepatitis may follow.

Viral (?) Dysentery.—A fairly extensive outbreak of epidemic nausea, vomiting and diarrhea has again been reported from England, beginning in May 1945, similar to those which occurred in this country.[150] Other epidemics have been reported in personal letters.[151] It is interesting to note how difficult it is to introduce a new term for a disease. The term "viral dysentery" was tentatively suggested[152] to imply dysentery (bad bowel) probably caused by a virus, but three editorial comments[153] on the paper referred to are entitled "Gastric Influenza," "Virus Dysentery" and "Virus Enteritis," respectively.

In an outbreak of epidemic diarrhea of the newborn the gamma globulin given to 28 infants had no preventive or curative effect.[154]

Pleurodynia.—Seventy-five patients with pleurodynia were studied in Alabama[155] between June and November 1944. Headache and paresthesias were often present in addition to the symptoms usually reported. It is hinted that a filtrable virus has been isolated from patients.

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148. Evans, W. F., and Graybiel, A.: Electrocardiographic Evidence of Cardiac Complications in Infectious Mononucleosis, Am. J. M. Sc. **211**:220-226 (Feb.) 1946.

149. Cohn, C., and Lidman, B. J.: Hepatitis Without Jaundice in Infectious Mononucleosis, J. Clin. Investigation **25**:145-151 (Jan.) 1946.

150. Brown, G.; Crawford, G. J., and Stent, L.: Outbreak of Epidemic Diarrhea and Vomiting in a General Hospital and Surrounding District, Brit. M. J. **2**:524-527 (Oct. 20) 1945.

151. Epidemic Diarrhoea and Vomiting, Letters, Brit. M. J. **2**:666 (Nov. 10) 1945.

152. Reimann, H. A.; Price, A. H., and Hodges, J. H.: The Cause of Epidemic Diarrhea, Nausea and Vomiting (Viral Dysentery?), Proc. Soc. Exper. Biol. & Med. **59**:8-9 (May) 1945.

153. "Gastric Influenza," editorial, Lancet **2**:342 (Sept. 15) 1945. Virus Dysentery editorial, J. A. M. A. **129**:518-519 (Oct. 13) 1945. Virus Enteritis, editorial, Lancet **1**:62-63 (Jan. 12) 1946.

154. High, R. H., and others: Further Observations of Epidemic Diarrhea of the Newborn, J. Pediat. **28**:407-417 (April) 1946.

155. Nichamin, S. J.: Clinical and Epidemiologic Aspects of Epidemic Pleurodynia, J. A. M. A. **129**:600-605 (Oct. 27) 1945.

BACILLARY DISEASES

Bacillary Dysentery.—The confusion in the nomenclature of bacillary dysentery continues. A paper entitled "Shiga Dysentery"[156] describes experiences with the disease cause by Shigella paradysenteriae. In most readers' minds "Shiga dysentery" implies infection with the Shiga type of bacilli as distinguished from the Flexner type and other strains of "paradysentery" bacilli. Even the prefix "para" is unsatisfactory. Perhaps the term "shigellosis," as suggested by others, is preferable for the group of diseases to which the name of the causative agent of any of the component members can be added.

In the paper referred to it is stated that sulfadiazine given in the first twenty-four hours of disease gives the best results. Symptomatic relief, however, does not always indicate cure of the intestinal lesions, which may persist for several weeks, especially if treatment with sulfadiazine is started late. The use of the sigmoidoscope is as essential to diagnosis and management in dysentery as the otoscope is in diseases of the ear. Sulfadiazine is preferable to other sulfonamide compounds, according to Hardy.[157]

In the experience of others,[158] in India, the clinical course of bacillary dysentery was not significantly affected by either sulfadiazine or sulfaguanidine. The alvine discharge and the duration of disease were the same in treated and in untreated patients. The lack of effect may be explained by the fact that treatment was often started too late, on the average five days after the onset; even so, many patients were treated on the first and second days. Another reason may be that the disease was mild; only 10 per cent were seriously sick, and none died. The authors also report that, contrary to general opinion, infection with Shigella dysenteriae was no more severe than infection with other members of the genus. Renal complications resulting from the use of sulfadiazine were common and often alarming.

Typhoid.—In an epidemic of typhoid 80 of 239 British soldiers who had had at least three yearly antityphoid vaccinations contracted the disease.[159] A few of them had received their last vaccination three weeks before the onset of the disease. The infection in those vaccinated was as severe as usual. The occurrence may cast grave doubt on the value of antityphoid vaccination, but vaccination, as the authors point out,

156. Smith, L. A.: Shiga Dysentery, J. A. M. A. **130**:18-22 (Jan. 5) 1946.

157. Hardy, A. V.: Studies of the Acute Diarrheal Diseases, Pub. Health Rep. **60**:1037-1042 (Sept. 7) 1945.

158. Elsom, K. A.; Pepper, D. S., and Forrester, J. S.: The Treatment of Bacillary Dysentery in Chinese Soldiers with Sulfaguanidine and Sulfadiazine, Am. J. M. Sc. **211**:103-109 (Jan.) 1946.

159. Jordan, J., and Everley, H.: Typhoid Fever in Immunized Personnel, Lancet **2**:333-335 (Sept. 15) 1945.

apparently prevented typhoid generally throughout the British Army, since no other similar outbreaks were reported. It is probable that the epidemic was caused by infection so massive as to break through the existent immunity. Similar experience was reported in studies on an outbreak in American troops in Guam.[160]

In this country an outbreak of typhoid was traced to orange juice prepared by a carrier.[161] Among 211 immunized persons who drank the juice only 1 contracted typhoid, while among 140 unvaccinated persons there were 17 attacks. Typhoid bacilli inoculated in orange juice remained viable at room temperature for six days.

Type specific bacteriophage was used with apparent success in the treatment of typhoid.[161a] The results need confirmation.

The typing of typhoid bacilli is now on a firm basis and is of great value in epidemiology. Of 1,485 cultures obtained in Georgia, 1,153 could be classified by the bacteriophage method.[162] Types A, E and C accounted for 72 per cent of them.

If a test proposed by Dennis and Saigh[163] is reliable, an important new diagnostic aid is at hand. According to the authors, the presence of an antigen of Eberthella typhosa can be demonstrated as early as the fifth day by the simple procedure of layering patient's serum on specific immune rabbit serum. A precipitate forms at the juncture. Absence of precipitate does not exclude typhoid.

Fowl is the greatest source of salmonella infection, or paratyphoid, and ducks and duck eggs are especially important. Evidence is now at hand implicating chicken eggs.[164] After an outbreak of "food poisoning" on a ship, Salmonella Montevideo was demonstrated as the internal contaminant of eggs.

Cholera.—In a paper[165] giving few technical details a naval unit reports amazing success in the treatment of cholera. All patients treated

160. Syverton, J. T., and others: Typhoid and Paratyphoid A in Immunized Military Personnel, J. A. M. A. **131**:507-514 (June 8) 1946.

161. Duncan, T. G., and others: Outbreak of Typhoid Fever with Orange Juice as the Vehicle, Illustrating the Value of Vaccination, Am. J. Pub. Health **36**:34-36 (Jan.) 1946.

161a. Knouf, E. G., and others: Treatment of Typhoid Fever with Type Specific Bacteriophage, J. A. M. A. **132**:134-137 (Sept. 21) 1946.

162. Morris, J. F.; Brin, A., and Sellers, T. F.: Types of Eberthella Typhosa Found in Georgia During the Four-Year Period 1941-1944, J. Infect. Dis. **77**: 25-27 (July-Aug.) 1945.

163. Dennis, E. W., and Saigh, A. S.: Precipitable Typhoid Bacterial Antigen in the Serum of Typhoid Fever Patients, Science **102**:280-282 (Sept. 14) 1945.

164. Watt, J.: An Outbreak of Salmonella Infection in Man from Infected Chicken Eggs, Pub. Health Rep. **60**:835-839 (July 20) 1945. Crowe, M.: Localized Outbreak of Salmonella Food Poisioning Apparently Transmitted by a Hen's Egg, J. Hyg. **44**:342-345 (May) 1946.

(Footnotes continued on next page)

with plasma and sulfadiazine or sulfaguanidine recovered. Great stress is placed on the value of plasma injected intravenously despite a warning in United States Army Technical Bulletin 138 that plasma and whole blood generally are not necessary and "may be very harmful." The great difference in the mortality rates of 95 per cent in one control group and zero in a treated group seems exaggerated. In my own experience in Chungking, China, the mortality rate was 5 per cent in 160 patients treated energetically with isotonic solution of sodium chloride and sodium bicarbonate solution alone.[166] Because of many circumstances, including malnutrition, age, complications, other disease and late treatment, it seems reasonable to expect a mortality rate of at least 5 per cent in a disease as severe as cholera, no matter what treatment is given. No significant benefit was noted from the use of sulfonamide compounds, nor from streptomycin except for slight shortening of the attacks. According to a recent report, cholera has again broken out in Chungking, Shanghai and elsewhere in Asia.

The low mortality rate just described for well treated patients is in striking contrast to the rate for the epidemic which broke out in British prisoners of war in Siam.[167] Of 1,600 troops, 173 had cholera, and of these 100 died, or 58 per cent. Patients lived under harrowing conditions. No facilities for treatment were available. Even under such circumstances the mortality rate was not so high as stated, since mild attacks were admittedly not included statistically. Cholera was diagnosed only if patients were dehydrated and in a shocklike state. In the absence of laboratory aid, other rampant diarrheal diseases, especially bacillary dysentery, could not be differentiated from cholera.

In persons vaccinated against cholera agglutinins for brucella often develop, which may cause diagnostic confusion, especially in regard to veterans returning from the Asiatic area.[168] The reaction may be an anamnestic one or an H antigen may be common to both Vibrio comma and Brucella.

An epidemic first thought to be epidemic nausea, vomiting and diarrhea, occurring in Illinois, on investigation appeared to be caused by a

165. Report on Cholera Studies in Calcutta: Value of Chemotherapy in Treatment of Cholera and Use of Blood Plasma in Cholera Collapse, Epidemiology Unit no. 50, U. S. Nav. M. Bull. **45**:1049-1053 (Dec.) 1945.

166. Reimann, H. A., and others: Asiatic Cholera: Clinical Study and Experimental Therapy with Streptomycin, Am. J. Trop. Med. **26**:631-647 (Sept.) 1946.

167. DeWardener, H. E.: Cholera Epidemic Among Prisoners of War in Siam, Lancet **1**:637-640 (May 4) 1946.

168. Eisele, C. W., and others: Development of Brucella Agglutinins in Humans Following Vaccination for Cholera, Proc. Soc. Exper. Biol. & Med. **61**:89-91 (Jan.) 1946.

vibrio, V. jejuni, which causes enteritis in cows.[169] Presumably milk was the source of the vibrios. These were from the feces and the blood of some of the patients.

Brucellosis.—Chronic brucellosis is no doubt a medical problem but not so great as to be a potential danger to national health, according to a recent statement.[170] Space forbids combating many of the dubious statements made in this fanciful paper, which reveals a lack of knowledge of fundamental features of brucellosis; deserved criticism appears elsewhere.[171] The endotoxin mentioned is hypothetic; the suggestion of performing cholecystectomy or splenectomy as therapy is unwarranted, and the criteria for diagnosis are insufficient. A positive cutaneous reaction alone cannot be relied on to establish the diagnosis. If the three complicated cases reported were selected as representative of cases of chronic brucellosis, one wonders how many of the 146 persons studied actually had the disease. According to Angle and his associates, brucellergin, on which the author depends so strongly, is not as reliable in cutaneous tests as heat-killed brucellas.[172]

Tularemia.—In the epidemiologic study of tularemia rabbits should be distinguished from rodents. About 90 per cent of human attacks of tularemia result from contacts with rabbits, of which the cottontail is the most important in North America.[173] Other rabbits, hares, rodents, sheep, game birds, other animals, ticks and deer flies account for the rest.

Stuart and Pullen[174] review the literature on tularemic pneumonia and on tularemic meningitis and report cases of their own. An outbreak of tularemia due to tick-borne Pasteurella tularensis occurred among troops during maneuvers in Tennessee in 1943.[175] Larson[176] found the bacteria in the sputum of 3 patients with tularemia, 2 without evidence

169. Levy, A. J.: A Gastro-Enteritis Outbreak Probably Due to a Bovine Strain of Vibrio, Yale J. Biol. & Med. **18**:243-258 (March) 1946.

170. Benning, H. M.: Chronic Brucellosis: Success of Treatment with Brucellin, J. A. M. A. **130**:320-325 (Feb. 9) 1946.

171. Goodman, M. J.: Chronic Brucellosis, Correspondence, J. A. M. A. **131**: 30 (May 4) 1946.

172. Harris, H. J.: Diagnosis of Undulant Fever, Queries and Minor Notes, J. A. M. A. **130**:546 (Feb. 23) 1946.

173. Jellison, W. L., and Parker, R. R.: Rodents, Rabbits and Tularemia in North America: Some Zoological and Epidemiological Considerations, Am. J. Trop. Med. **25**:349-362 (July) 1945.

174. Stuart, B. M., and Pullen, R. L.: Tularemic Pneumonia: Review of American Literature and Report of Fifteen Additional Cases, Am. J. M. Sc. **210**: 223-236 (Aug.) 1945; Tularemic Meningitis: Review of Literature and Report of Case, with Postmortem Observations, Arch. Int. Med. **76**:163-166 (Sept.) 1945.

175. Warring, W. B., and Ruffin, J. S.: Tick-Borne Epidemic of Tularemia, New England J. Med. **234**:137-140 (Jan. 31) 1946.

176. Larson, C. L.: Isolation of Pasteurella Tularensis from Sputum, Pub. Health Rep. **60**:1049-1053 (Sept. 7) 1945.

of pulmonary involvement and the third with only roentgenographic evidence of it. It seems therefore that in making a diagnosis of tularemia the sputum should be inoculated into mice as a routine procedure.

Tetanus.—Boyd [177] reviews experience with tetanus as encountered during the war by physicians of the British Army. The incidence of the disease was negligible as compared with that in former wars. Reports of 103 cases were assembled. In only 22 cases was the patient a person who had been actively immunized, but the mortality rate in those who had been actively immunized did not fall below the usual level. The rate, however, was lower in those actively immunized who were given prophylactic antitoxin in addition; 100,000 units of antitoxin given intravenously within thirty-six hours after the first symptoms seemed to lower the mortality rate. Sedatives relieved symptoms but did not influence the course of the disease.

Pratt [178] reemphasizes the unsatisfactory state of the therapy of tetanus. In severe attacks treatment was ineffective, and most patients with mild attacks recovered. There was no evidence that 80,000 units of antitoxin was more effective than 30,000 units. Fatal reactions occurred when antitoxin was injected intrathecally in some patients who might otherwise have recovered; intrathecal therapy is not recommended. Excision of the site of infection, as expected, had no effect on the course of the disease.

Penicillin is of no value in the treatment of tetanus unless secondary invasion with bacteria sensitive to it takes place.[179]

Diphtheria.—Delp and his associates [180] suggest that many patients now regarded as having the Guillain-Barré syndrome (virus encephalomyelitis) or infectious polyneuritis actually have diphtheritic paralysis. They report details of 5 cases. Their suggestion is important, for diphtheria has lost popularity, so to speak, and is not often in the modern physician's mind. Particularly confusing are cases of diphtheria of the skin.

Diphtheria is still a serious menace. It is among the chief causes of death in central Europe and in Japan.[181] Its incidence is increasing in

177. Boyd, J. S. K.: Tetanus in the African and European Theater of War, 1939-1945, Lancet **1**:113-119 (Jan. 26) 1946.

178. Pratt, E. L.: Clinical Tetanus, J. A. M. A. **129**:1243-1247 (Dec. 29) 1945.

179. Altemeier, W. A.: Penicillin in Tetanus, J. A. M. A. **130**:67-72 (Jan. 12) 1946.

180. Delp, M. H.; Sutherland, G. F., and Hashinger, E. H.: Post-Diphtheritic Polyneuritis: A Report of Five Cases with Albuminocytologic Dissociation Simulating Guillain-Barré Syndrome, Ann. Int. Med. **24**:618-628 (April) 1946.

181. Diphtheria Still Leading Epidemic Disease, Miscellaneous Topics, J. A. M. A. **130**:89 (Jan. 12) 1946.

Germany and Finland. In Britain and Hungary, where immunization is possible, there are fewer cases.

Tuberculosis.—Biggs [182] reemphasizes the subclinical nature of first attacks of tuberculosis. The diagnosis of a primary infection can be made only by a history of recent exposure and a tuberculin test. Serial roentgenograms aid in following its course. The author again raises the controversial question whether allergy is a beneficial or a harmful factor and plans to pursue the study further.

Dock [183] explains why tuberculosis so often attacks the upper lobes of the lungs: The erect position of man tends to reduce the amount of blood in the upper parts of the lungs. Perhaps this also accounts for the beneficial effects of prolonged rest in bed, since the flow of blood in the areas affected is increased by a recumbent position.

In spite of the fact that the Calmette-Guérin, or BCG, vaccine has been studied as a preventive of tuberculosis for more than twenty-five years, the reports of its value have been inconclusive. A recent study of 3,000 American Indians was made extending over a period of six years.[184] BCG vaccine was given to 1,550, and the rest served as controls. The results were encouraging; among the controls 48 died of tuberculosis in the six year period, compared with 9 of the vaccinated persons. BCG vaccine was used with great success in Denmark.[184a] Mycobacterium tuberculosis from voles is a distinct strain but gives protection against other mammalian strains of tubercle bacilli when used as a vaccine. The vole strain vaccine was as effective as BCG vaccine in experimental studies.[184b]

Dubos [185] reports a method by which Mycobacterium tuberculosis can be grown in seventy-two hours in Long's synthetic medium containing small amounts of phosphatides and esters of polyhydric alcohols. Other studies [186] show that certain water-soluble esters of fatty acids

182. Biggs, A. D.: A Roentegn Ray and Clinical Study of Primary Tuberculosis, Arch. Int. Med. **77**:393-404 (April) 1946.

183. Dock, W.: Apical Localization of Phthisis: The Significance in Treatment of Prolonged Rest in Bed, Am. Rev. Tuberc. **53**:297-306 (April) 1946.

184. Aronson, J. D., and Palmer, C. E.: Experience with BCG Vaccine in the Control of Tuberculosis Among North American Indians, Pub. Health Rep. **61**:802-820 (June 7) 1946.

184a. Holm, J.: Tuberculosis Control in Denmark, Pub. Health Rep. **61**: 1426-1443 (Oct. 4); 1298-1315 (Sept. 6) 1946.

184b. Birkhaug, O. K.: Immunization with the Vole Bacillus, Am. Rev. Tuberc. **53**:411-418 (May) 1946.

185. Dubos, R.: Rapid and Submerged Growth of Mycobacteria in Liquid Media, Proc. Soc. Exper. Biol. & Med. **58**:361-362 (April) 1945.

186. Dubos, R., and Davis, B. D.: Factors Affecting the Growth of Tubercle Bacilli in Liquid Media, J. Exper. Med. **83**:409-423 (May) 1946.

increased the amount of growth. Serum albumin added to synthetic liquid mediums causes abundant growth in eleven to fifteen days.

Hamsters, once said to be suitable for routine diagnostic tests for tuberculosis, have been found highly resistant to a virulent strain of a human type of tubercle bacilli which caused widespread tuberculosis of guinea pigs.[187]

Leprosy.—Many attempts have already been made to improve the unsatisfactory clinical classification of leprosy. Arnold and Tilden[188] propose one which seems to reconcile different points of view. They suggest the term "lepromatous leprosy" to include types which are generally strongly positive bacteriologically, have a bad prognosis, are relatively communicable, have a negative cutaneous reaction to lepromin and histologically show granulomatous tissue with bacillus-laden histiocytes. The term "tuberculoid leprosy" describes those which are usually negative bacteriologically, have a good prognosis, are slightly if at all communicable, have a positive cutaneous reaction to lepromin and histologically show tubercle-like aggregations of epithelioid cells and lymphocytes.

Although its specificity for Mycobacterium leprae cannot be demonstrated, Promin is at present the drug of choice in the treatment of leprosy.[189] Significant improvement occurred in 137 patients treated by Faget and Pogge. Improvement is slow but is evident after six months or more of intravenous injections given in courses. Promizole (4,2'-diaminophenyl-5-thiazolsulfone) and Diasone (disodium formaldehyde sulfoxylate diaminodiphenylsulfone) are also of value in therapy.[190]

Bubonic Plague.—An epidemic of plague broke out in Dakar, French West Africa, involving more than 500 people.[191] Other outbreaks occurred in Taranto, Italy, and in Corsica. The disease was apparently imported by infected rats that had gained access to ships. Thirteen cases with 10 deaths occurred in Taranto in May and June 1945. The outbreaks were controlled by extermination of rats, by treatment of vermin

187. Steenken, W., and Wagley, P. F.: Comparison of the Golden Hamster to the Guinea Pig Following Inoculation of Virulent Tubercle Bacilli, Proc. Soc. Exper. Biol. & Med. **60**:255-257 (Nov.) 1945.

188. Arnold, H. L., and Tilden, I. L.: The Classification and Nomenclature of Leprosy with Suggestions for a Simplification of Both, Ann. Int. Med. **23**:65-73 (July) 1945.

189. Faget, G. H., and Pogge, R. C.: The Therapeutic Effect of Promin in Leprosy, Pub. Health Rep. **60**:1165-1171 (Oct. 5) 1945.

190. Faget, G. H.: Pogge, R. C., and Johansen, F. A.: Promizole Treatment of Leprosy, Pub. Health Rep. **61**:957-960 (June 28) 1946; Present Status of Diazone in the Treatment of Leprosy, ibid. **61**:960-963 (June 28) 1946.

191. Rotman, C. M. H.: Bubonic Plague in Dakar, J. Roy. Nav. M. Serv. **31**:155-158 (July) 1945. Epidemic of Plague in Corsica, Foreign Letters, J. A. M. A. **130**:964 (May 6) 1946.

with DDT powder (2,2-bis-(parachlorophenyl)-1,1,1-trichloroethane) and by use of vaccine. The use of DDT powder to control fleas and of sodium fluoroacetate (1080) to kill rats successfully stopped an epidemic of plague in Peru.[191a] A list of reported cases of plague and deaths therefrom in the United States from 1900 to 1944 is published.[192]

Three fatal cases of melioidosis are reported among soldiers of the United States, 2 in Guam and 1 in Burma.[193] Penicillin was ineffective.

COCCAL DISEASES

Subacute Bacterial Endocarditis.—Loewe and his associates [194] report the recovery of a strain of streptococci now designated as Streptococcus s. b. e. in 39 per cent of 106 cultures from patients with subacute bacterial endocarditis. These streptococci formed a rather homogeneous group mostly of one serologic type. A similar strain has thus far not been found in the oropharynx. It is highly resistant to penicillin. Others [195] find that streptococci isolated from patients and called alpha, or green-producing, streptococci are serologically identical and frequently belong to Lancefield's group D, as do most enterococci.

Meningococcic Meningitis.—Penicillin and sulfonamide compounds control the acute purulent reactions in patients with meningococcic meningitis, but unfortunately do not always prevent the coincident or the subsequent development of fibroblasts and scar tissue.[196] Therefore, neurologic sequels, such as paralysis, deafness and aphasia, still occur in treated patients.

Rheumatic Fever.—As may have been expected, evidence accumulates to oppose massive salicylate medication, which once was recommended by Coburn. In addition to the fatalities reported last year, further serious toxic reactions occurred when 350 micrograms of

191a. Macchiavello, A.: Plague Control with DDT and "1080": Results Achieved in a Plague Epidemic at Tumbes, Peru, 1945, Am. J. Pub. Health **36**:842-854 (Aug.) 1946.

192. Hampton, B. C.: Plague Infection Reported in the United States During 1944, and Summary of Human Cases, 1900-1944, Pub. Health Rep. **60**:1361-1365 (Nov. 16) 1945.

193. Mirick, G. S., and others: Melioidosis on Guam, J. A. M. A. **130**:1063-1067 (April 20) 1946. Cox, C. D., and Arbogast, J. L.: Melioidosis, Am. J. Clin. Path. **15**:567-570 (Dec.) 1945.

194. Loewe, L., and others: Streptococcus s.b.e. in Subacute Bacterial Endocarditis, J. A. M. A. **130**:257 (Feb. 2) 1946.

195. Wheeler, S. M., and Foley, G. E.: Note in Serologic Classification of Streptococci Isolated from Subacute Bacterial Endocarditis, Am. Heart J. **30**:511-513 (Nov.) 1945.

196. Bailey, P.: Chronic Leptomeningeal Thickening Following Treatment of Meningitis with Sulfa Drugs, Ann. Surg. **122**:917-925 (Dec.) 1945.

salicylate per cubic centimeter of serum was attained.[197] There is also little advantage gained by giving the drug intravenously instead of by the oral route. According to Murphy,[198] characteristic lesions of rheumatic pneumonia, tendon sheath nodules, tenosynovitis and an episcleral nodule developed while the amounts of salicylate in the serum rested between 300 and 600 micrograms. In one patient rheumatic activity developed in a joint for the first time during salicylate therapy. Since the drug has long been known to have no influence on the proliferative reaction of the disease or on its course and duration, serving only to relieve the symptoms, there is no point of giving more than just enough to produce comfort. Manchester [197b] records 25 mg. of salicylate per 100 cc. of serum as satisfactory to suppress rheumatic activity. The amount is usually attained by giving from 10 to 12 Gm. of acetylsalicylic acid or of sodium salicylate together with 8 Gm. of sodium bicarbonate orally. Patients with heart failure are given aminopyrine daily until compensated, then sodium salicylate. He recommends intravenous medication in severe attacks or in those refractory to oral medication.

Guerra [199] gives the following theory to account for the clinical effect of salicylate relieving the symptoms of rheumatic fever. Strains of hemolytic streptococci are known to produce or possess hyaluronidase. The substance increases the spread of dyes when injected into tissue by decreasing viscosity which favors the passage of exudates and pathogenic bacteria. When sodium salicylate is given, it greatly inhibits the spreading effect of hyaluronidase and may thereby cause its beneficial effect in rheumatic fever.

If a new drug, succinyl acid benzyl ester, gives the beneficial effects described in recent report, it may supplant other "antirheumatic" agents.[200] The results have not been confirmed.

According to two groups of investigators,[201] the electrocardiographic changes which follow postscarlatinal arthritis and carditis are the same

197. (*a*) Wegria, R., and Smull, K.: Salicylate Therapy in Acute Rheumatic Fever, J. A. M. A. **129**:485-490 (Oct. 13) 1945. (*b*) Manchester, R. C.: Rheumatic Fever in Naval Enlisted Personnel, ibid. **131**:209-213 (May 18) 1946.

198. Murphy, G. E.: Salicylate and Rheumatic Activity: Objective Clinical Histological Study of Effect of Salicylate on Rheumatic Lesions, Those of the Joints and Tendon Sheaths in Particular, Bull. Johns Hopkins Hosp. **77**:1-42 (July) 1945.

199. Guerra, F.: Hyaluronidase Inhibition by Sodium Salicylate in Rheumatic Fever, Science **103**:686-687 (June 7) 1946.

200. Gubner, R., and Szucs, M.: Therapeutic Measures for Rheumatic Fever, New England J. Med. **233**:652-656 (Nov. 29) 1945.

201. Watson, R. F.; Rothbard, S., and Swift, H. F.: The Relationship of Postscarlatinal Arthritis and Carditis to Rheumatic Fever, J. A. M. A. **128**:

as those noted in cases of rheumatic fever. This suggests that in both instances they are streptococcic in origin. There are also no differences in the serum protein pattern revealed by electrophoresis as between rheumatic fever and scarlet fever. Steinmann,[202] a Swiss, believes that scarlatinal and rheumatic carditis are different.

Rantz and his co-workers [203] believe that rheumatic fever is always a sequel to infection with hemolytic streptococci and that a continuing, potentially serious nonarthritic disease may occur as well. The presence or the absence of tonsils is of variable importance in different epidemics of streptococcic infection.

In a food-borne epidemic caused by type 1 hemolytic streptococci, nearly all the persons who became carriers of these cocci were sick. Most of them had follicular tonsillitis, but many mild attacks occurred which would not have been recognized as streptococcic infection if special laboratory studies had not been made. Patients who had had a previous attack of streptococcic infection seldom reacted with more than minimal clinical signs to reinfection with a new strain. It is possible that this type of mild infection may precede rheumatic fever and account for instances heretofore reported in which previous infection with hemolytic streptococci was supposedly absent or in which rheumatic fever seemed to be preceded by various nonstreptococcic conditions. The nature and the degree of pharyngeal tissue reaction to infection with hemolytic streptococci are highly variable and not necessarily related to the severity of the clinical response. It is obvious also that the eventual control of rheumatic fever will depend on the prevention and the control of infection with hemolytic streptococci.

Patients convalescing from rheumatic fever probably do not need so long a period of convalescence as is usually believed to be necessary. In one study [204] patients convalescent from acute rheumatic fever were given graded exercises as soon as their clinical condition permitted. The usual laboratory criteria of recovery were not depended on. In another study,[205] made at Randolph Field, Texas, patients could safely

1145-1152 (Aug. 18) 1945. Dole, V. P.; Watson, R. F., and Rothbard, S.: The Electrophoretic Changes in the Serum Protein Patterns of Patients with Scarlet Fever and Rh Fever, J. Clin. Investigation **24**:648-656 (Sept.) 1945. Rantz, L. A.; Spink, W. W., and Boisvert, P. J.: Hemolytic Streptococcus Sore Throat, Arch. Int. Med. **76**:278-283 (Nov.-Dec.) 1945; Abnormalities in the Electrocardiogram Following Hemolytic Streptococcus Sore Throat, ibid. **77**:66-79 (Jan.) 1946.

202. Steinmann, B.: Das Herz beim Scharlach, Berne, Hans Huber, 1945.

203. Rantz, L. A.; Boisvert, P. J., and Spink, W. W.: The Etiology and Pathogenesis of Rheumatic Fever, Arch. Int. Med. **76**:131-137 (Sept.) 1945.

204. Robertson, H. F.; Schmidt, R. E., and Feiring, W.: Therapeutic Value of Early Physical Activity in Rheumatic Fever, Am. J. M. Sc. **211**:67-75 (Jan.) 1946.

205. Karpovich, P. V., and others: Physical Reconditioning After Rheumatic Fever, J. A. M. A. **130**:1198-1203 (April 27) 1946.

participate in graded exercises two weeks after the cessation of rheumatic activity. In both studies it was observed that the exercises improved the mental outlook of the patient, and caused no harmful effects.

Although rheumatic fever is said to be rare in tropical climates, the disease is not uncommon in Panama.[206] Because numerous attacks have recently been recognized and older clinicians emphasized the danger of such a happening, it is suggested that the incidence of rheumatic fever has increased in Panama since 1927. No reason therefor is evident. Rheumatic heart disease is present also among the natives of New Guinea [207] and among those of Curaçao,[208]

A puzzling precipitation which occurs when serum taken from a patient early in an attack of rheumatic fever is mixed with serum taken during the acute phase or during convalescence was thought to be a specific reaction.[209] Further tests, however, showed that the reaction occurs, though less frequently, in other diseases as well. Whether the precipitate results from nonspecific changes in the albumin-globulin ratio or from formation of an auto-antigen-antibody system is unknown.

In a paper entitled "Direct Culture of Rheumatic Virus," the authors [210] caution readers not to be misled by the title. It seems that the blood of a patient with rheumatic fever contained something which produced peculiar transmissible changes in inoculated eggs, namely, thickening of the chorioallantois and redness of the embryo.

RICKETTSIAL DISEASES

There is a close relationship between the distribution of the Nuttall species of cottontail rabbits and the distribution of Rocky Mountain spotted fever in the western part of the United States.[211] That species may be the important reservoir of infection in this region. Other

206. Hardgrove, M.; Whittier, L., and Smith, E. R.: Rheumatic Fever on the Isthmus of Panama, J. A. M. A. **130**:488-490 (Feb. 23) 1946.

207. Levine, H. D.: Rheumatic Heart Disease in New Guinea, Including a Cardiovascular Survey of Two Hundred Native Papuans, Ann. Int. Med. **24**:827-836 (May) 1946.

208. Hartz, P. H., and Van der Sar, A.: Occurrence of Rheumatic Carditis in the Native Population of Curaçao, Netherlands West Indies, Arch. Path. **41**: 32-38 (Jan.) 1946.

209. Wedum, A. G., and Wedum, B. G.: Serum Precipitation Reaction in Rheumatic Fever and in Other Conditions, Proc. Soc. Exper. Biol. & Med. **61**: 432-438 (April) 1946.

210. MacNeal, W. J., and others: Direct Culture of Rheumatic Virus, Science **103**:620-621 (May 17) 1946.

211. Jellison, W. L.: The Geographical Distribution of Rocky Mountain Spotted Fever and Nuttall's Cottontail in the Western United States, Pub. Health Rep. **60**:958-961 (Aug. 17) 1945.

species of cottontails are present in all areas where the disease has been recognized. Para-aminobenzoic acid was effective in the treatment of the disease experimentally established in guinea pigs,[212] but penicillin was of no value.[213] In a survey in Texas 3.5 per cent of 4,219 persons had complement-fixing antibodies for murine typhus, suggesting that many more cases of typhus occur than are recognized.[214]

Tsutsugamushi Disease.—The whole May 1945 issue of the *American Journal of Hygiene* is devoted to tsutsugamushi disease, giving a summary of the studies made in the New Guinea area. The disease, also known as scrub typhus, is widespread over an enormous area. The mites Trombicula fletcheri and Trombicula walchi, like Trombicula akamushi, which live on rodents, also carry Rickettsia orientalis, the causative agent. In experimental studies both immune rabbit serum [215] and para-aminobenzoic acid [216] were effective therapeutically. Tsutsugamushi disease has been recognized in the Philippine Islands for the first time.[217] The mortality rate among 240 patients was 4.5 per cent.

Para-aminobenzoic acid is effective for three rickettsial diseases: typhus,[217a] Rocky Mountain spotted fever and tsutsugamushi. According to Greiff's theory,[218] the therapeutic effect is due to the drug's stimula-

212. Anigstein, L., and Bader, M. N.: Para-Aminobenzoic Acid: Its Effectiveness in Spotted Fever in Guinea Pigs, Science **101**:591-592 (June 8) 1945.

213. Fitzpatrick, F. K.: Penicillin in Experimental Spotted Fever, Science **102**:96-97 (July 27) 1945.

214. Davis, D. E., and Pollard, M.: Prevalence of Typhus Complement-Fixing Antibodies in Human Serums in San Antonio, Texas, Pub. Health Rep. **61**:928-931 (June 21) 1946.

215. Topping, N. H.: Tsutsugamushi Disease (Scrub Typhus): The Effects of an Immune Rabbit Serum in Experimentally Infected Mice, Pub. Health Rep. **60**:1215-1220 (Oct. 12) 1945.

216. Murray, E. S.; Zarafonetis, C. J. C., and Snyder, J. C.: Further Report on Effect of Para-Aminobenzoic Acid in Experimental Tsutsugamushi Disease, Proc. Soc. Exper. Biol. & Med. **60**:80-84 (Oct.) 1945. Snyder, J. C., and Zarafonetis, C. J. D.: Effects of Para-Aminobenzoic Acid in Experimental Tsutsugamushi Disease, ibid. **60**:115-117 (Oct.) 1945. Tierney, N. A.: Effect of Para-Aminobenzoic Acid in Tsutsugamushi Disease, J. A. M. A. **131**:280-285 (May 25) 1946.

217. Philip, C. B.; Woodward, T. E., and Sullivan, R. R.: Tsutsugamushi Disease (Scrub or Mite-Borne Typhus) in the Philippine Islands During American Re-Occupation in 1944-45, Am. J. Trop. Med. **26**:229-242 (March) 1946.

217a. Smith, P. K.: The Use of Para-Aminobenzoic Acid in Endemic (Murine) Typhus, J. A. M. A. **131**:1114-1117 (Aug. 3) 1946.

218. Greiff, D.; Pinkerton, H., and Moragues, V.: Defect of Enzyme Inhibitors and Activators on the Multiplication of Typhus Rickettsia: I. Penicillin, Para-Aminobenzoic Acid, Sodium Fluoride and Vitamins of the B Group, J. Exper. Med. **80**:561-574 (Dec.) 1944.

tion of the host cells' metabolism which probably interferes with the intracellular multiplication of the rickettsias.

Q Fever.—Several explosive outbreaks of pneumonia occurred among British and American troops in Greece and Italy.[219] In one unit 36 per cent of the personnel were sick. Each outbreak was related in some way to the living quarters or other locality of those who were sick. There was no evidence of person to person infection, and the period of incubation was about two weeks. A rickettsia was isolated, and serologic studies suggested that it was related to Q fever. An epidemic occurred in March 1946 in Texas,[220] affecting 40 employees of a stockyard and meat packing plant. Variations in degree of severity were noted from mild influenza-like disease to severe pneumonia. Two patients died. Cattle were suspected to be the source of the infection.

Another outbreak of Q fever, affecting 26 persons, occurred in a laboratory.[221] The infection was thought to have been air borne. Persons who actually worked with the disease did not contract it. Apparently they had acquired immunity. The July 1946 issue of the *American Journal of Hygiene* contains twelve papers on the subject.

Pollard and others[222] report experiments which support their previous observations that Bullis fever is caused by a transmissible agent which can be cultured in the chick embryo. The agent originated from ticks near Camp Bullis in Texas. Minute coccobacillary bodies were found in lymphoid cells, unlike those described in Colorado tick fever, from which Bullis fever is different immunologically as well. They also found Colorado tick fever to differ immunologically from dengue. Despite many similarities the two are probably different diseases. A denguelike fever has been observed for the first time in Puerto Rico.[223]

Further studies on Colorado tick fever show that it is caused by a virus which passes through membranes of 24 millimicron porosity.[224]

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219. Outbreaks of a Rickettsial Disease Related to Q Fever, Bull. U. S. Army M. Dept. **5**:245-246 (March) 1946.

220. Irons, J. V., and others: Outbreak of Q Fever, in the United States, Pub. Health Rep. **61**:784-785 (May 31) 1946.

221. Outbreak of Q Fever Among Bethesda Research Workers, Washington Letter, J. A. M. A. **130**:720 (March 16) 1946.

222. Pollard, M.; Livesay, H. R.; Wilson, D. J., and Woodland, J. C.: Experimental Studies with Bullis Fever, Am. J. Trop. Med. **26**:175-187 (March) 1946; Immunological Studies of Dengue Fever and Colorado Tick Fever, Proc. Soc. Exper. Biol. & Med. **61**:396-398 (April) 1946.

223. Diaz-Rivera, R. S.: A Bizarre Type of Seven Day Fever Clinically Indistinguishable from Dengue, Bol. Asoc. méd. Puerto Rico **38**:75-80 (March) 1946.

224. Florio, L.; Stewart, M. O., and Mugrage, E. R.: The Etiology of Colorado Tick Fever, J. Exper. Med. **83**:1-10 (Jan.) 1946.

SPIROCHETAL DISEASES

Relapsing Fever.—Eleven cases of relapsing fever caused by Spirochaeta recurrentis were observed in Texas.[225] In several instances this sickness was confused with other diseases but the diagnosis was established when the spirochete was observed in the blood during the febrile episode and, in 1 instance in sections of a cutaneous lesion during the afebrile period. Oxophenarsine hydrochloride did not prevent relapses and gave disappointing results in 7 patients. Penicillin was said to be more effective in 2 patients. Experience [226] with relapsing fever, probably caused by S. recurrentis, in India indicates that better results are obtained with arsenical therapy. Oxophenarsine hydrochloride was used.

Penicillin was as effective as neoarsphenamine in an outbreak in Tunisia[227] but the latter is cheaper and easier to give. Penicillin is preferable if jaundice is present.

Rat Bite Fever.—Penicillin is reported to have been of value in rat bite fever caused by Streptobacillus moniliformis; 5 cases were studied.[228] In a case caused by Spirillum minus, the spirillum was demonstrated in the lymph of the primary wound for the first time. Swyer [229] reports a case of rat bite fever caused by the bite of a cat. Penicillin was said to have been curative.

Spirochetal Jaundice.—Jaundice due to Leptospira icterohaemorrhagiae, or Weil's disease, affected at least 17 British soldiers who had bathed in the River Arno or in the water of bomb craters.[230] Five died. Patients treated with penicillin or with antileptospiral serum did not show any beneficial effect as compared with untreated patients. Although many attacks of infectious hepatitis occurred at the same time there, the authors said they had practically no difficulty in diagnosis of either disease, but one wonders how mild cases of leptospirosis, particularly nonicteric ones, can be so easily differentiated. Evidence of

225. Taft, W. C., and Pike, J. B.: Relapsing Fever: Report of a Sporadic Outbreak, Including Treatment with Penicillin, J. A. M. A. **129**:102-104 (Dec. 8) 1945.

226. Wolff, B. P.: Asiatic Relapsing Fever: Report of One Hundred and Thirty-Four Cases Treated with Mapharsen, Ann. Int. Med. **24**:203-216 (Feb.) 1946.

227. Greaves, F. G.; Gezon, H. M., and Alston, W. F.: Louse-Borne Relapsing Fever in Tunisia, U. S. Nav. M. Bull. **45**:1029-1048 (Dec.) 1945.

228. Watkins, C. G.: Ratbite Fever, J. Pediat. **28**:429-448 (April) 1946.

229. Swyer, G. I. M.: Rat Bite Fever Due to Cat Bite: Satisfactory Response to Penicillin After Failure of Arsenotherapy, Brit. M. J. **2**:386-388 (Sept. 22) 1945.

230. Hutchinson, J. H., and others: Outbreak of Weil's Disease in the British Army in Italy, Brit. M. J. **1**:81-83 (Jan. 19) 1946.

nephritis without jaundice may be the predominant manifestation of the disease.[230a]

Contrary to previous reports, not all strains of white mice are susceptible to infection with L. icterohaemorrhagiae when inoculated for diagnosis.[231]

Swine and cattle are now incriminated as carriers of leptospiras, and they transmit the organisms to man. Gsell in Switzerland [232] studied swineherd's disease, which is characterized by serous meningitis and formerly was thought to be viral in origin. He found agglutinin for Leptospira pomona in high titer. Sixty-five per cent of hogs tested also had the agglutinin in high titer, and L. pomona was in the urine of 2. He quotes Clayton, of Australia, as having demonstrated L. pomona in dairy workers. Probably a similar or an identical agent was recognized in Russia and in Palestine, where Bernkopf [233] called it Leptospira bovis.

PROTOZOAL DISEASES

Malaria.—Plasmodium vivax malaria caused the Kahn flocculation test for syphilis to show a positive reaction in 33 and a doubtful reaction in 11 of 100 cases of malaria.[234] The test became negative in 84 per cent in four weeks, and negative in all cases at eleven weeks. No change occurred in the spinal fluid.

Reports [235] have appeared concerning the toxic effects of quinacrine hydrochloride (atabrine): an "atabrine dermatitis complex," aplastic anemia, neutropenia, hepatitis and toxic psychosis. The mortality rate has been high. In spite of these rare occurrences, the value of the drug outweighs the untoward effects attributed to it.

Attempts have been made to provide a better drug. A new compound called M. 4888, or paludrine, (N_1-p-chlorophenyl-N_5 isopropyl biguanide) is reported from England.[236] In daily doses of 10 to 15 mg.

230a. Stiles, W. W.; Goldstein, J. D., and McCann, W. S.: Leptospiral Nephritis, J. A. M. A. **131**:1271-1274 (Aug. 17) 1946.

231. Stavitksy, A. B., and Green, R. G.: Susceptibility of the Young White Mouse (Mus Musculus) to Experimental Leptospirosis, Science **102**:352-353 (Oct. 5) 1945.

232. Gsell, O.: Disease of Swineherds Caused by Leptospira Pomona, Presse méd. **53**:525-526 (Sept. 29) 1945.

233. Infection with Bovine Leptospirosis in Man in Palestine, Foreign Letters, J. A. M. A. **131**:250 (May 18) 1946.

234. Robinson, H. M., and McKinney, W. W.: The Effect of Vivax Malaria on Spinal Fluid and Blood Serologic Tests for Syphilis, J. A. M. A. **129**:667-668 (Nov. 3) 1945.

235. Untoward Reactions Attributable to Atabrine, Special Article, J. A. M. A. **129**:1091-1093 (Dec. 15) 1945.

236. Triumph Against Malaria, Brit. M. J. **2**:653-654 (Nov. 10) 1945.

it effectively terminates benign tertian malaria but does not prevent relapse. In daily doses of 0.1 Gm. it effectively prevents clinical signs of malaria but does not prevent infection. It is said to be superior to both quinine and quinacrine hydrochloride and, unlike the latter, does not stain the skin yellow. Not enough trial has been made to learn what possible toxic effect may follow its use.

Similar statements may be made about chloroquine, studied by Americans.[237] This drug is also said to be an effective suppressive. It is said to cause abrupt ending of a clinical attack of P. vivax malaria and to cure Plasmodium falciparum malaria in one or two days. It does not discolor the skin. Pentaquine (SN 13,276) is too toxic as a suppressive agent but, together with quinine, cures severe infection due to P. vivax.[237a] According to recent unpublished information, a reevaluation shows plasmochin and related compounds to be the most effective agents used to prevent relapses in malaria, although toxic effects are relatively common.

Further study following Coggeshall's demonstration of an immune reaction of monkeys to malaria shows that these animals can be partially protected against Plasmodium knowlesi infection with a vaccine composed of killed parasites together with oily substances and killed tubercle bacilli.[238]

Most and Hayman [239] point out the bizarre clinical forms in which P. vivax malaria may occur. Especially puzzling from the point of view of diagnosis will be malaria in returned service men in whom the disease was suppressed so long as quinacrine hydrochloride was taken. The disease may first appear a year afterward and assume diverse clinical forms. It may cause signs and symptoms resembling appendicitis and cholecystitis; there may be nausea, vomiting and diarrhea; urticaria may develop; pneumonia may be suspected. It must also be remembered that patients who have had malaria may actually have appendicitis, cholecystitis, tonsillitis, pneumonia and other diseases.

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237. Wartime Research in Malaria, Board for the Coordination of Malarial Studies, Science **103**:8-9 (Jan. 4) 1946. Loeb, R. F., and others: Activity of Antimalarial Agent Chloroquine (SN 7618), J. A. M. A. **130**:1069-1070 (April 20) 1946. Most, H., and others: Chloroquinone for Treatment of Vivax Malaria, ibid. **131**:963-967 (July 20) 1946.

237a. Loeb, R. F.: Activity of a New Antimalarial Agent, Pentaquine (SN 13,276), J. A. M. A. **132**:321-323 (Oct. 12) 1946.

238. Freund, J., and others: Immunization of Rhesus Monkeys Against Malarial Infection (P. Knowlesi) with Killed Parasites and Adjuvants, Science **102**:202-204 (Aug. 24) 1945.

239. Most, H., and Hayman, J. M.: Uncommon Clinical Manifestations of Vivax Malaria, J. A. M. A. **130**:480-485 (Feb. 23) 1946.

Experiments on patients showed that anoxia as experienced at high altitudes did not cause relapse or parasitemia in persons recently recovered from malaria.[240]

Kala Azar.—Kala azar in military personnel who have served in endemic areas may give diagnostic difficulties if it develops after their return home. Months may elapse after infection before symptoms begin. Two instances are reported in England in which soldiers who returned from the Mediterranean area with the infection had only slight fever, malaise, splenomegaly and leukopenia many months after their exposure in North Africa.[241] The title of the author's paper is misleading; his patients were not asymptomatic, but they did not reveal their symptoms until questioned.

Packchanian [242] reports 2 cases of kala azar occurring in American soldiers who had served in the Near East. The diagnosis can be made only after the organism has been cultivated from a lesion of the skin or from the blood, the bone marrow, the spleen or the liver and identified. Since the diagnosis cannot be made by examining stained smears alone, in which yeast or other extraneous material may be mistaken for Leishmania, both Packchanian and Wenyon question Benedek's diagnosis of the first supposed autochthonous case in the United States.

According to South American physicians, an autochthonous case of American visceral leishmaniasis was reported by Penna in 1934.[243] Tavares reported the first diagnosis made during life and now reports a second. A new species, Leishmania chagasi, is described, No details are given as to how the diagnosis was proved or how closely L. chagasi is related to Leishmania donovani or Leishmania tropica.

Van Dyke and Gellhorn [244] tested a large number of antimonial and other compounds to find a more effective therapeutic agent for leishmaniasis, but none was superior to diethylaminoethanol of sodium antimony gluconate (Stibanose), stibamine glucoside (Neostam) or ethylstibamine (Neostibosan), which are now in use.

Kala azar is characterized by hyperinosemia, yet amyloid disease has not been reported to be present during this infection. Amyloid disease often occurs in mice inoculated with L. donovani.[245]

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240. Howe, C. D., and Duffe, F. L.: Effect of Altitude Anoxia in Provoking Relapse in Malaria, Science **103**:223 (Feb. 22) 1946.

241. Armstrong, T. G.: Asymptomatic Kala-Azar in Soldiers from Over-Seas, Brit. M. J. **2**:918 (Dec. 29) 1945.

242. Packchanian, A.: Leishmaniasis, J. A. M. A. **129**:544-547 (Oct. 20) 1945.

243. American Visceral Leishmaniasis, Foreign Letters, J. A. M. A. **129**: 761-762 (Nov. 10) 1945.

244. Van Dyke, H. B., and Gellhorn, A.: Chemotherapy of Experimental Leishmaniasis, Proc. Soc. Exper. Biol. & Med. **61**:403-405 (April) 1946.

245. Gellhorn, A., and others: Amyloidosis in Hamsters with Leishmaniasis, Proc. Soc. Exper. Biol. & Med. **61**:25-30 (Jan.) 1946.

American Trypanosomiasis.—Two soldiers contracted American trypanosomiasis (Chagas' disease) in Panama and were seriously sick.[246] Prominent articular symptoms resembled those of rheumatic fever. Lymphocytosis was present. Stibophen (Fuadin) seemed to have therapeutic value.

Coccidiosis.—Human coccidiosis (Isospora hominis infection) is rare but is thought to have caused the symptoms of diarrhea, abdominal pain and eosinophilia of 3 patients.[247] Isospora was present in the stools. It is usually hard to be sure whether the organisms are pathogens or saprophytes.

METAZOAL DISEASES

The problem of the control of trichinosis is discussed by Gould,[248] who calculates that the average American during his lifetime eats about two hundred meals of pork containing trichinas. Each of these would be harmless if the pork were properly cooked, but many chances of infection persist. Although most of the pork (70 per cent) available is processed under federal inspection, the larger part of the total supply is likely to be infected. The most important factor in the control of the disease is the eradication of the infected hogs. The incidence of trichinosis of hogs (1.5 per cent) has not been changed in fifty years. The incidence of infection in Germany was 0.001 per cent and that in Denmark much less.

Filariasis.—Coggeshall [249] reviews the important features of filariasis as these pertain to military personnel stationed in areas in which the disease is endemic. Although about 38,000 men were exposed, the infection was diagnosed in only about 10,000. The disease was usually mild and characterized in its early stage by lymphopharyngitis, lymphedema, lymphadenitis and funiculitis, as well as by aches and pains in the major lymphatic areas. Elephantiasis or other disabling effects did not occur and probably will not, because the infection was light. The filarias cannot multiply in infected patients unless they undergo further passage in mosquitoes, and there is little chance that they will survive in this country. There are no reliable specific therapeutic agents.

After patients are removed from the areas in which the disease is endemic, the infection disappears, and they are usually symptom free.

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246. Moseley, V., and Miller, H.: South American Trypanosomiasis (Chagas' Disease), Arch. Int. Med. **76**:219-229 (Oct.) 1945.

247. Humphrey, A. A.: Isospora Hominis Infection in Man, J. A. M. A. **130**:143-145 (Jan. 19) 1946.

248. Gould, S. E.: An Effective Method for the Control of Trichinosis in the United States, J. A. M. A. **129**:1251-1254 (Dec. 29) 1945.

249. Coggeshall, L. T.: Filariasis in the Serviceman: Retrospect and Prospect, J. A. M. A. **131**:8-12 (May 4) 1946.

Incapacitating sequels were observed in only 0.2 per cent of Zeligs'[250] patients and in 3 of the 532 patients of Behm and Hayman.[251]

The diagnosis was often made without the causative organisms being demonstrated. Laboratory tests other than that for eosinophilia are seldom helpful. Filarias are rarely found.[252]

Moniliasis.—A patient with pulmonary moniliasis recovered promptly after being treated with small amounts of specific immune serum—which represents a new idea concerning the therapy of mycotic disease.[253] There is, however, little proof that the disease was moniliasis. The diagnosis was based on a reaction of the skin to an injection of immune rabbit serum and a culture of sputum which showed Candida albicans, but there is no mention of smears showing the presence of this organism. A skin test with the monilia elicited no significant reaction, and specific agglutinins did not develop until after the patient had been treated with the immune serum.

Reiter's Disease.—Reiter's disease, characterized by urethritis, conjunctivitis, arthritis and diarrhea, may be mistaken for gonorrhea. Twenty-five cases of a disease resembling Reiter's were reported by Hollander and co-workers[254] from an Army hospital for patients with arthritis. The literature on the subject was collected and reviewed by Vallee.[255] While the cause is unknown, studies by Dienes[256] point to organisms of the pleuropneumonia group. These were found in the prostatic secretion of 4 patients with the syndrome and in the synovial fluid of 1. The Stevens-Johnson syndrome is like Reiter's disease except for a cutaneous eruption and stomatitis. Two cases are reported by Kove.[257] An epidemic of epididymo-orchitis of unknown cause occurred among soldiers in Malta characterized by two phase fever and unilateral testicular swelling.[258] It was not caused by brucellosis or by sandfly fever.

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250. Zeligs, M. A.: Psychosomatic Aspects of Filariasis, J. A. M. A. **128**: 1139-1142 (Aug. 18) 1945.

251. Behm, A. W., and Hayman, J. M.: The Course of Filariasis After Removal from an Endemic Area, Am. J. M. Sc. **211**:385-394 (April) 1946.

252. Hodge, I. G.; Denhoff, E., and Vanderveer, J. B.: Early Filariasis (Bancrofti) in American Soldiers, Am. J. M. Sc. **210**:207-222 (Aug.) 1945.

253. Hiatt, J. S., and Martin, D. S.: Recovery from Pulmonary Moniliasis Following Serum Therapy, J. A. M. A. **130**:205-206 (Jan. 26) 1946.

254. Hollander, J. L., and others: Arthritis Resembling Reiter's Syndrome: Observation on Twenty-Five Cases, J. A. M. A. **129**:593-595 (Oct. 27) 1945.

255. Vallee, B. L.: Reiter's Disease: Review of Literature, with Presentation of a Case, Arch. Int. Med. **77**:295-306 (March) 1946.

256. Dienes, L.; Smith, C., and Ropes, M. W.: Studies of the Incidence and Pathogenicity of Pleuropneumonia-like Organism in Humans, read at the meeting of the American Society of Clinical Investigation, May 27, 1946.

257. Kove, S.: Stevens-Johnson Syndrome (Eruptive Fever with Stomatitis and Conjunctivitis), Am. J. M. Sc. **210**:611-623 (Nov.) 1945.

MISCELLANEOUS

Origin of Viruses.—Two monographs have been published which are of importance to all who are interested in infections. One is by Dubos [259]; the other, by Burnet.[260] Burnet subscribes to the view that viruses are living forms which have evolved, by parasitic degeneration, from larger micro-organisms, such as bacteria, fungi or protozoa. Unless viruses are in a biologic class by themselves, it would seem that this theory runs counter to general evolutionary procedure in which organisms seem to evolve by gaining various powers and increasing in complexity. There would seem to be as much logic in the opposite view that viruses, by mutation, are the source of higher forms of life, as follows—viruses→ psittacosis group→ rickettsias→ bacteria→ protozoa, fungi and others. Although it is now well known that certain bacteria have filtrable variant forms—for example, the pleuropneumonia organisms and Bacillus tularensis (Foshay)—there is no evidence that any of these variants should be regarded as true filtrable viruses.

Burnet also holds that all or nearly all the known virus diseases of man have been derived from animals. Psittacosis, St. Louis encephalitis, equine encephalitis and Q fever, he suggests, are "new" diseases, all having appeared in the last fifty years, but just because these diseases have been recognized recently by the development of new knowledge and technic does not mean that they have not been prevalent but unrecognized for centuries. Nevertheless, it is possible that genuinely new infections may arise from time to time by the appearance of mutant forms among known viruses or bacteria, which may find in man an environment suitable for their growth.

Bacterial Variation.—Although the phenomenon of bacterial variation has been studied for many years, it has seemed to be chiefly a matter of academic interest. There is no evidence that recovery from infectious disease depends primarily on a change from virulence to avirulence of bacteria, but there seems to be no doubt that the instability of most bacteria and their constant changing into various forms is of practical importance from the standpoint of epidemiology, etiology and diagnosis and in the preparation of vaccines.[261]

There is also no doubt but that variation of form causing the colonies to differ from the usual ones may at times prevent their recognition

258. Tunbridge, R. E., and Gavey, C. J.: Epidemic Epididymo-Orchitis in Malta, Lancet **1**:775-779 (May 25) 1946.

259. Dubos, R. J.: The Bacterial Cell, Harvard University Monograph in Medicine and Public Health no. 6, Cambridge, Mass., 1945.

260. Burnet, F. M.: Virus as Organism, Harvard University Monograph in Medicine and Public Health no. 8, Cambridge, Mass., 1945.

261. Reimann, H. A.: The Significance of Bacterial Type Transformation in Infectious Diseases and Epidemiology, Tr. A. Am. Physicians **53**:270-273, 1938.

on diagnostic culture mediums. For example, "small colony forms" of typhoid bacilli isolated from patients with typhoid may not be recognized as such without further study because of their unusual smallness. Chronic carriers of Vibrio comma are thought not to exist, but perhaps carriers shed V. comma in a variant phase in which the organisms grow in unrecognizable colonies.

Morton and Shoemaker [262] now report the recovery of small colony variants of gonococci from 3 patients with gonorrhea. These colonies composed of gram-negative cocci were five to ten times smaller than the usual ones and would ordinarily not be suspected of being colonies of Neisseria gonorrheae. On serial culture, however, they reverted to the usual colony forms.

Diet and Resistance.—Important studies on the relation of diet to the power to resist infection were made by Schneider and Webster.[263] In extensive experiments the natural resistance of mice to Salmonella enteritidis was best maintained by a diet of whole wheat and dried milk, in which the "natural" elements, or "immunogen," in whole wheat were the more important.

In other studies,[264] rats and mice given a diet deficient in thiamine were more susceptible to oral infections with Salmonella typhi murium than those given an adequate diet. In mice the diminished resistance was specifically due to the deficiency of thiamine, but in rats the inanition which accompanies avitaminosis was responsible. The experiments provide further evidence that one cannot generalize in regard to the effect of avitaminosis on susceptibility to various infections, as previously shown in experiments with poliomyelitis. Different species of animals behave differently.

Pyridoxine deficiency impedes the development of antibodies.[265] Antibody production depends on an adequate supply of essential amino acids,[266] yet in certain experiments,[265] animals fed restricted amounts of food developed antibody titers fivefold higher than animals given an unlimited diet.

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262. Morton, H. E., and Shoemaker, J.: The Identification of Neisseria Gonorrheae by Means of Bacterial Variation and the Detection of Small Colony Forms in Clinical Material, J. Bact. **50**:585-587 (Nov.) 1945.

263. Schneider, H. A., and Webster, L. T.: Nutrition of the Host and Natural Resistance to Infection, J. Exper. Med. **81**:359-384 (April) 1945.

264. Guggenheim, K., and Beuchler, E.: Thiamin Deficiency of Rats and Mice to Infection wtih Salmonella Typhi Murium, Proc. Soc. Exper. Biol. & Med. **61**:413-416 (April) 1946.

265. Stoerck, H. C., and Eisen, H. N.: Suppression of Circulating Antibodies in Pyridoxine Deficiency, Proc. Soc. Exper. Biol. & Med. **62**:88-89 (May) 1946.

266. Wissler, R. W.; Woodridge, R. L., and Steffee, C. H.: Influence of Amino Acid Feeding upon Antibody Production, Proc. Soc. Exper. Biol. & Med. **62**:199-203 (June) 1946.

Book Reviews

Protozoology. By Richard R. Kudo, D.Sc. Third Edition. Price, $8. Pp. 778, with 336 illustrations. Springfield, Ill.: Charles C Thomas, Publisher, 1944.

Although written by a zoologist and not primarily for physicians, this book seems admirably suited for the physician who wishes to pursue the subject in more than the most superficial way. The first hundred and ninety pages of the book deal interestingly with such general matters as ecology, morphology, physiology and reproduction; the remainder of the book is a systematic discussion of protozoa. The innumerable excellent drawings are an outstanding feature.

Virus as Organism: Evolutionary and Ecological Aspects of Some Human Virus Diseases. By Frank MacFarlane Burnet, M.D., F.R.S. Harvard University, the Edward K. Dunham Lectures for the Promotion of the Medical Sciences, 1944. Harvard University Monographs in Medicine and Public Health [Number 8]. Price, $2. Pp. 134. Cambridge, Mass.: Harvard University Press, 1945.

The subtitle of this book, "Evolutionary and Ecological Aspects of Some Human Virus Diseases," summarizes the contents. The first three chapters discuss reproduction, variation and survival of viruses in general, evolution and change in virus disease and the reaction of the host to virus infection. Several important virus diseases are discussed from the point of view of the ecologic interaction of the two species, virus and man. Dr. Burnet concludes that each of these diseases has its own individuality and must be studied in detail as far as practical measures are concerned. The possibilities in speculation about the origin of viruses are discussed. The dominant view seems to be that they evolve by parasitic degeneration from larger micro-organisms, probably bacteria.

The book is of particular interest to workers in virus research and to public health administrators. There is a bibliography of one hundred and twenty articles.

The Osseous System: A Handbook of Roentgen Diagnosis. By V. W. Archer, M.D. Price, $5.50. Pp. 320, with 148 plates. Chicago: The Year Book Publishers, Inc., 1945.

This handy book covers in a comprehensive manner roentgenology of the osseous system. The left hand pages contain the text, and the right hand pages, reproductions of roentgenograms. These photographs, though small, are good reproductions and seem to illustrate well the points brought out in the text. The book should be useful not only to radiologists but also to general physicians.

Oral Medicine. By Lester W. Burket, D.D.S., M.D. Price, $12. Pp. 674. Philadelphia: J. B. Lippincott Company, 1946.

The author of this book, widely experienced in the medical aspects of dentistry, has undertaken to bring together under one cover the oral manifestations of practically all the diseases to which the human body is heir. The result is a scholarly, readable, well documented and beautifully illustrated work which no dentist can afford not to read and which will be a valuable reference for physicians wishing to identify obscure lesions of the mouth or desiring to review all possible oral manifestations of systemic diseases.

After introductory chapters on medicodental relations, oral consultation and general laboratory procedures, the author begins a series of sections, the first of

which covers diseases generally considered intrinsic to the mouth, such as oral fusospirochetosis, heavy metal stomatitis, lingual diseases and gingivitis and the oral aspects of dermatology. Then follow sections on the general medical diseases, grouped under the headings organ systems, metabolism and infectious granulomas.

One might take issue with many statements in the book, such as one on page 227, in which the author, in speaking of angina pectoris, said, "This syndrome may precede typical coronary artery disease" and one on page 234, in which it is stated that stenosis of the pulmonary veins occurs in the tetralogy of Fallot. The color atlas consists of sixty well selected and beautifully reproduced photographs. The book should prove invaluable to dentists as a review of clinical medicine and it is an excellent source of information on oral aspects of disease for the physician.

News and Comment

ANNUAL CONVENTION OF THE AMERICAN ACADEMY OF ALLERGY

The American Academy of Allergy will hold its annual convention at Hotel Pennsylvania, New York city, November 25 to 27, inclusive. All physicians interested in allergic problems are cordially invited to attend the sessions as guests of the Academy without payment of a registration fee. The program has been arranged to cover a wide variety of conditions in which allergic factors may be important. Papers will be presented dealing with the latest methods of diagnosis and treatment, as well as with the results of investigation and research. Advance copies of the program may be obtained by writing to the Chairman on Arrangements, Dr. Horace S. Baldwin, 136 East 64th Street, New York City, before November 10.

APPOINTMENTS

Dr. Richard A. Kern, formerly professor of clinical medicine and chief of the outpatient department and the allergy section of the Hospital of the University of Pennsylvania, has been appointed professor and head of the department of medicine, Temple University School of Medicine, Philadelphia, to succeed Dr. Charles L. Brown.

CORRECTION

In the article by Dr. Norman Rosenthal, Dr. Sidney P. Zimmerman and Dr. Shepard Shapiro entitled "Prothrombin Level of Peripheral Blood and Sternal Marrow" in the April issue (ARCH. INT. MED. **77**:420, 1946), "not" was inadvertently inserted in the first paragraph of the "Conclusions." The paragraph should read as follows:

"From the evidence presented we are led to conclude that prothrombin is not elaborated by the reticuloendothelial system and therefore is probably a function of the hepatic parenchyma."